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TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS

THIRTY-EIGHTH SESSION

HELD AT ATLANTIC CITY, N. J.

MAY 1 AND 2, 1923

1875.33.
19.2.24.

VOLUME XXXVIII

PHILADELPHIA
PRINTED FOR THE ASSOCIATION
1923

NOTICE

The Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings.

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DORNAN, PRINTER
701–709 ARCH STREET
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1889.	Francis Minot.	R. Palmer Howard. / S. C. Busey.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1890.	S. C. Busey.	William Pepper. / Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1891.	Wm. Pepper.	Henry M. Lyman.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1892.	Henry M. Lyman.	George Ross.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1893.	A. L. Loomis.	Reginald H. Fitz.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1894.	Reginald H. Fitz.	William Osler.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1895.	Wm. Osler.	A. Jacobi.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1896.	A. Jacobi.	J. M. Da Costa.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1897.	J. M. Da Costa.	F. C. Shattuck.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1898.	F. C. Shattuck.	G. Baumgarten.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1899.	G. Baumgarten.	E. G. Janeway.	I. Minis Hays.	Henry Hun.	W. W. Johnston.
1900.	E. G. Janeway.	Wm. H. Welch.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1901.	Wm. H. Welch.	H. P. Walcott.	I. Minis Hays.	Henry Hun.	J. P. C. Griffith.
1902.	James C. Wilson.	Jas. Stewart.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1903.	James Stewart.	W. T. Councilman.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1904.	W. T. Councilman.	E. L. Trudeau.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1905.	E. L. Trudeau.	Frank Billings.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
1906.	Frank Billings.	F. P. Kinnicutt.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
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1908.	James Tyson.	V. C. Vaughan.	S. Solis Cohen.	Henry Hun.	J. P. C. Griffith.
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1910.	Henry Hun.	F. Forchheimer.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1911.	F. Forchheimer.	J. George Adami.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
1912.	J. George Adami.	L. F. Barker.	S. Solis Cohen.	Geo. M. Kober.	J. P. C. Griffith.
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1900. Ewing, James, 260 West 57th St., New York.
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1920. Finley, Frederick G., 273 Bishop St., Montreal, Canada.
1921. Fitz, R., 721 Huntington Ave., Boston.
1895. Flexner, Simon, Rockefeller Institute, 66th Street and Avenue A, New York.
1913. Ford, W. W., 1134 Cathedral St., Baltimore, Md.
1916. Foster, Nellis B., 121 East 62d St., New York.
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1914. Gay, Frederick P., University of California, Berkeley.
1922. Giffin, H. Z., Mayo Clinic, Rochester, Minn.
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1923. Graham, D., 1 Queen's Park, Toronto, Ontario.
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1890. Griffith, J. P. Crozer, 1810 Spruce St., Philadelphia.
1922. Gwyn, N. B., 48 Bloor St., E., Toronto, Ontario.
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1914. Howard, Campbell P., Iowa City, Iowa.
1911. Howard, W. T., 1213 N. Calvert St., Baltimore.
1911. Howland, John, Johns Hopkins Hospital, Baltimore, Md.
1916. Hunt, J. Ramsay, 20 W. 50th St., New York.
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1917. Irons, Ernest E., 122 S. Michigan Ave., Chicago.
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1916. Jobling, James W., Dept. of Pathology, Columbia University, New York.
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1916. Karsner, Howard T., Lakeside Hospital, Cleveland.
1915. Klotz, Oskar, University of Toronto, Toronto, Ontario.
1900. Koplik, Henry, 30 East 62d St., New York.
1920. Krause, A. K., The Hopkins Hospital, Baltimore.
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1923. Lambert, A., 43 E. 72d St., New York.
1906. Lambert, Samuel W., 130 East 35th St., New York.
1915. Landis, H. R. M., 1817 Pine St., Philadelphia.
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1921. Lewis, P. A., Rockefeller Institute, Princeton, N. J.
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1909. Longcope, Warfield T., Johns Hopkins Hospital, Baltimore.
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1905. McCrae, Thomas, 1929 Spruce St., Philadelphia.
1919. McLean, F. C., Peking Union Medical College, 61 Broadway, New York.
1919. McLester, J. S., Empire Building, Birmingham, Ala.
1905. Macallum, A. B., McGill University, Montreal, Canada.
1902. MacCallum, W. G., The Hopkins Hospital, Baltimore.
1920. MacLeod, J. J. R., University of Toronto, Toronto, Ont.
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1905. Miller, Joseph L., 122 S. Michigan Boulevard, Chicago.
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1917. Mosenthal, Herman O., 49 E. 53rd St., New York.
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1919. Newburgh, L. N., University Hospital, Ann Arbor, Mich.
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1902. Opie, E. L., 600 S. Kingshighway, St. Louis, Missouri.
1918. Ordway, T., Albany Medical College, Albany, N. Y.
1919. Palmer, W. W., 41 E. 70th St., New York.
1899. Park, Wm. H., 315 West 76th St., New York.
1916. Peabody, Francis W., 50 Brimmer St., Boston.
1922. Pepper, O. H. P., 16th and Walnut Sts., Philadelphia.
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1923. Richards, A. N., University of Pennsylvania, Philadelphia.
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1915. Robinson, G. Canby, The Johns Hopkins Hospital, Baltimore, Md.
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1916. Rous, Peyton, 131 E. 19th St., New York.
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1908. Sailer, Joseph, 1718 Spruce St., Philadelphia.
1919. Sellards, A. W., Harvard Medical School, Boston.
1902. Sippy, B. W., 122 S. Michigan Avenue, Chicago, Ill.
1907. Sollmann, Torald H., 1353 E. 9th St., Cleveland, Ohio.

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1898. Stengel, Alfred, 1728 Spruce St., Philadelphia.
1889. Stockton, Charles G., 436 Franklin St., Buffalo, N. Y.
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1923. Strouse, S., 104 S. Michigan Ave., Chicago.
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1897. Thayer, W. S., 1208 Eutaw Place, Baltimore.
1889. Thompson, W. Gilman, 17 W. 53d St., New York.
1912. Tileston, Wilder, 101 Grove St., New Haven.
1922. Van Slyke, D.D., Rockefeller Institute, 66th St. and Ave. A, New York.
1914. Wadsworth, Augustus B., 278 Yates St., Albany.
1922. Walker, I. C., Peter Bent Brigham Hospital, Boston.
1920. Warfield, L. M., University of Michigan, Ann Arbor, Mich.
1901. Warthin, Aldred S., University of Michigan, Ann Arbor, Mich.
1906. Weaver, George H., 629 S. Wood St., Chicago.
1918. Webb, G. B., Colorado Springs, Col.
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1913. Whipple, Geo. H., University of Rochester, Rochester, N. Y.
1917. White, Franklin W., 322 Marlborough St., Boston.
1923. White, P. D., Massachusetts General Hospital, Boston.
1918. White, S. M., 1009 Nicollet Ave., Minneapolis, Minn.
1915. White, Wm. Charles, Cosmos Club, Washington, D. C.
1912. Wilson, Louis B., 1101 W. Zumbro St., Rochester, Minn.
1918. Wolbach, S. B., Harvard Medical School, Boston, Mass.
1917. Wood, Edward J., 201 Chestnut St., Wilmington, N. C.
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1916. Woodyatt, Rollin T., 104 S. Michigan Ave., Chicago.
1921. Zinsser, H., 162 E. 74th St., New York.

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1922. Blankenhorn, M. A., Lakeside Hospital, Cleveland, Ohio.
1923. Bloomfield, A. L., The Johns Hopkins Hospital, Baltimore.
1921. Chesney, A. M., 7 W. Hamilton St., Baltimore.
1922. Drinker, C. K., Harvard Medical School, Boston.
1922. Geyelin, H. K., 33 E. 68th St., New York.
1922. Guthrie, C. G., Lawrenceville, N. J.
1923. Keith, N. M., Mayo Clinic, Rochester, Minn.
1921. Kilgore, E. S., University of California Hospital, San Francisco.
1921. Kolmer, J. A., Med. Dept., University of Penna., Philadelphia.
1920. Macht, D. I., Johns Hopkins Medical School, Baltimore.
1923. Maclachean, W. W. G., 1133 Wightman St., Pittsburgh.
1922. Marine, D., Montefiore Hospital, New York.
1922. Marriott, W. M., 500 S. Kingshighway, St. Louis.
1923. Mason, E. H., Royal Victoria Hospital, Montreal, Quebec.
1920. Moss, W. L., Harvard Medical School, Boston.
1921. O'Hare, J. P., 536 Commonwealth Ave., Boston.
1923. Oppenheimer, B. S., 124 E. 61st St., New York.
1923. Paullin, J. B., Doctor's Bldg., Atlantic, Ga.
1922. Scott, R. W., City Hospital, Cleveland.
1920. Vanderhoof, D., Professional Building, Richmond, Va.
1921. Williamson, C. S., 25 E. Washington St., Chicago.
1923. Wilson, F. N., 804 Lawrence St., Ann Arbor, Mich.

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* Original Members

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	1920.	Heger, Prof. Paul, University of Brussels, Brussels, Belgium.
*1886.	1915.	Hun, Henry, 149 Washington Ave., Albany.
1902.	1916.	Kober, Geo. M., 1819 Q St., N. W., Washington.
	1920.	Marchiafava, Prof. Ettore, Rome, Italy.
*1886.	1913.	Prudden, T. Mitchell, 160 W. 59th St., New York.
	1920.	Roux, Prof. E., Pasteur Institute, Paris, France.
1892.	1920.	Smith, Theobald B., Princeton, N. J.
1889.	1915.	Vaughan, Victor C., University of Michigan, Ann Arbor.
*1886.	1913.	Welch, William H., 807 St. Paul St., Baltimore.

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ELECTED	
1923.	Chauffard, Prof. A., University of Paris, Paris, France.
1923.	Elliott, Prof. T. R., U. C. H. Medical School, University St., London, W. C. I., England.
1923.	Rolleston, Sir H. D., 55 Upper Brook St., London W. I., England.
1923.	Widal, Prof. F., University of Paris, Paris, France.

EMERITUS MEMBERS

* Original Members

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1894.	1922.	Adami, J. G., Univ. of Liverpool, Liverpool, England.
1905.	1918.	Babcock, R. H., 30 N. Michigan Ave., Chicago.
1908.	1919.	Baldwin, E. R., Saranac Lake, New York.
1895.	1923.	Billings, Frank, 1550 N. State Parkway, Chicago.
1898.	1916.	Blackader, A. D., 236 Mountain St., Montreal.
1892.	1916.	Bolton, Meade B., Charlottesville, Va.
1898.	1917.	Brannan, John W., 48 W. 51st St., New York.
1888.	1910.	Bridge, Norman, 10 Chester Place, Los Angeles, Cal.
1899.	1923.	Cabot, R. C., 1 Marlborough St., Boston.
1889.	1916.	Cary, Charles, 340 Delaware Ave., Buffalo.
*1886.	1906.	Councilman, Wm. T., 78 Bay State Road, Boston.
1897.	1905.	Cushny, Arthur C., University of Edinburgh, Edinburgh, Scotland.
1894.	1908.	Cutler, Elbridge G., 214 Beacon St., Boston.
1888.	1916.	Dana, Charles L., 53 W. 53d St., New York.
1893.	1923.	Dock, G., Chamber of Commerce Bldg., Pasadena, Cal.
1901.	1919.	Edwards, A. R., 104 S. Michigan Ave., Chicago.
1890.	1902.	Fisk, S. A. Brimfield, Mass.
*1886.	1900.	Guitéras, John, Havana, Cuba.
*1886.	1902.	Hays, I. Minis, 268 S. 21st St., Philadelphia.
1897.	1910.	Hektoen, Ludvig, 637 S. Wood St., Chicago.
1900.	1917.	Holt, L. E., 14 W. 55th St., New York.
1890.	1902.	Hurd, H. M., Johns Hopkins Hospital, Baltimore.
1899.	1914.	James, Walter B., 17 W. 54th St., New York.
1895.	1918.	Lafleur, H. A., 215 Peel St., Montreal, Canada.
1888.	1919.	Lewis, M. J., 1316 Locust St., Philadelphia.
1891.	1920.	McPhedran, A., 151 Bloor St., W., Toronto, Can.
1898.	1916.	Mallory, F. B., Boston City Hospital, Boston.
1891.	1900.	Mason, A. Lawrence, 265 Clarendon St., Boston.
1919.	1922.	Meakins, J. C., Dept. of Therapeutics, Edinburgh University, Edinburgh, Scotland.

ELECTED ACTIVE MEMBER	ELECTED EMERITUS MEMBER	
1901.	1913.	Morse, John L., 70 Bay State Road, Boston.
1891.	1918.	Northrup, W. P., 61 E. 73d St., New York.
1904.	1920.	Pearce, R. M., Rockefeller Foundation, 61 Broadway, New York.
1898.	1914.	Pfaff, Franz, Dresdner Bank, Berlin.
*1886.	1898.	Polk, Wm. M., 7 East 36th St., New York.
1903.	1918.	Preble, R. B., 590 Dearborn Ave., Chicago.
1904.	1923.	Richardson, M. W., 67 Milk St., Boston.
*1886.	1904.	Robinson, Beverley, 42 West 37th St., New York.
1911.	1923.	Russell, F. F., Room 2701, 61 Broadway, New York.
1900.	1914.	Sears, Geo. G., 19 Marlborough St., Boston, Mass.
1900.	1921.	Sewall, Henry, 1360 Vine St., Denver, Col.
*1886.	1912.	Shattuck, Frederick C., 135 Marlborough Street, Boston.
1887.	1911.	Starr, M. Allen, 5 West 54th St., New York.
1907.	1920.	Taylor, A. E., University of Penna., Philadelphia.
1899.	1918.	Thacher, J. S., 20 W. 50th St., New York.
1898.	1918.	Vickery, H. F., Ipswich, Mass.
1889.	1904.	Walcott, Henry P., 11 Waterhouse St., Cambridge, Mass.
1894.	1920.	Williams, F. H., 505 Beacon St., Boston.
1901.	1922.	Williams, H. U., University of Buffalo, Buffalo, N. Y.
*1886.	1911.	Wilson, James C., 1509 Walnut St., Philadelphia.
1899.	1912.	Wright, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

DECEASED MEMBERS

* Original Members

DATE OF ELECTION

1896. Adler, Isaac, New York.
*1886. Atkinson, I. E., Baltimore.
*1886. Ball, A. Brayton, New York.
1890. Barker, Fordyce, New York.
*1886. Baumgarten, G., St. Louis.
1894. Biggs, H. M., New York.
*1886. Billings, John S., New York.
*1886. Bowditch, Henry I., Boston.
*1886. Bruen, Edward T., Philadelphia.
*1886. Busey, Samuel C., Washington, D. C.
1907. Carroll, James, Washington, D. C.
*1886. Chew, Samuel C., Baltimore.
*1886. Clark, Alonzo, New York.
*1886. Clymer, Meredith, New York.
*1886. Da Costa, J. M., Philadelphia.
1889. Dabney, William C., University of Virginia.
*1886. Dalton, John C., New York.
*1886. Dana, Israel T., Portland, Maine.
1888. Danforth, I. N., Chicago.
*1886. Delafield, Francis A., New York.
*1886. Donaldson, Frank, Baltimore.
*1886. Draper, William H., New York.
*1886. Edes, R. T., Reading, Mass.
1899. Ely, John Slade, New Haven, Conn.
1888. Ernst, H. C., Boston.
1895. Fischel, William E., St. Louis.
*1886. Fitz, Reginald H., Boston.
*1886. Folsom, Chas. F., Boston.
*1886. Forchheimer, F., Cincinnati.
*1886. Formad, Henry F., Philadelphia.
1894. Fussell, M. H., Philadelphia.
1889. Geddings, W. H., Atken, S. C.
1916. Gorgas, W. C., Washington.

DATE OF ELECTION

*1886. Graham, J. E., Toronto, Canada.
*1886. Henry, F. P., Philadelphia.
1898. Herter, C. A., New York.
*1886. Howard, R. Palmer, Montreal, Canada.
*1886. Hudson, Jr., E. Darwin, New York.
*1886. Hutchinson, James H., Philadelphia.
*1886. Jacobi, A., New York.
*1886. Janeway, E. G., New York.
1908. Janeway, T. C., Baltimore.
*1886. Johnson, Hosmer A., Chicago.
1899. Johnston, W. G., Montreal, Canada.
*1886. Johnston, W. W., Washington, D. C.
1902. Kelly, A. O. J., Philadelphia.
*1886. Kinnicutt, Francis P., New York.
1901. Kinyoun, J. J., Washington.
1890. Latimer, Thomas S., Baltimore.
*1886. Leidy, Joseph, Philadelphia.
*1886. Longstreth, Morris, Cambridge, Mass.
*1886. Loomis, Alfred L., New York.
1889. Loving, Starling, Columbus, O.
*1886. Lyman, Henry M., Chicago.
*1886. McBride, Thomas A., New York.
1914. McCrae, John, Montreal, Canada.
1890. MacDonnell, R. P., Montreal, Canada.
1887. Meigs, Arthur V., Philadelphia.
1892. Meltzer, S. J., New York.
*1886. Metcalfe, John T., Cold Springs, N. Y.
*1886. Miles, F. T., Baltimore.
*1886. Minot, Francis, Boston.
1898. Mitchell, John K., Philadelphia.
*1886. Mitchell, S. Weir, Philadelphia.
1887. Musser, John H., Philadelphia.
*1886. Osler, Sir William, Oxford.
1898. Packard, Frederick A., Philadelphia.
*1886. Peabody, George L., Newport, R. I.
*1886. Pepper, William, Philadelphia.
1888. Prentiss, D. W., Washington, D. C.
*1886. Putnam, James J., Boston.
1896. Reed, Walter, Washington, D. C.
1887. Reeves, James E., Chattanooga, Tenn.
*1886. Rochester, Thomas F., Buffalo, N. Y.
1889. Roosevelt, J. West, New York.

DATE OF ELECTION

*1886. Ross, George, Montreal, Canada.
1893. Rotch, Thomas M., Boston.
*1886. Schmidt, H. D., New Orleans.
*1886. Shattuck, G. B., Boston.
*1886. Sinkler, Wharton, Philadelphia.
*1886. Smith, A. A., New York.
1891. Smith, Andrew H., New York.
1915. Southard, E. E., Boston.
1905. Steele, J. Dutton, Philadelphia.
*1886. Sternberg, Geo. M., Washington.
1896. Stewart, D. D., Philadelphia.
*1886. Stewart, James, Montreal, Canada.
*1886. Stillé, Alfred, Philadelphia.
*1886. Thacher, James K., New Haven, Conn.
1899. Thacher, J. S., New York.
1889. Thomson, W. H., New York.
*1886. Trudeau, Edward L., Saranac Lake.
*1886. Tyson, James, Philadelphia.
*1886. Ward, Samuel B., Albany.
1898. Wesbrook, F. F., Vancouver.
*1886. Whittaker, James T., Cincinnati.
*1886. Wilkins, George, Montreal.
1898. Withington, Charles F., Boston.
*1886. Wood, H. C., Philadelphia.

ASSOCIATION
OF
AMERICAN PHYSICIANS

CONSTITUTION

As Amended May 3, 1922

ARTICLE I

OBJECT AND NAME

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

ARTICLE II

MEMBERS

The number of active members shall be limited to two hundred. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

An active member whose membership has extended throughout ten years or more may, at his request, be transferred by the Council to emeritus membership.

There shall be also a class of associate members, limited in number to twenty-five, from which class active members may be elected. These associate members shall each be elected for a term of five years and shall enjoy all the privileges of emeritus members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Provided, That in case of removal of an active member to a locality so distant that his attendance at the annual meetings may reasonably be regarded as impossible, the Council may be empowered, should it so desire, to transfer the name of such a member during his absence to the list of emeritus members, without regard to the length of his previous active membership.

There shall be a class of Corresponding Members, not to exceed twenty-five in number, to which distinguished physicians in countries other than the United States and Canada may be elected. The names of those proposed for this membership shall be put in nomination at an annual meeting by two active members, and the Council shall report those nominations which are approved by it to the next annual meeting for election. An affirmative vote of three-quarters of the members present shall be necessary for election. Corresponding Members shall be entitled to take part in the proceedings but not to vote.

ARTICLE III

OFFICERS

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually; five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elected at the annual meeting immediately following the Congress.

ARTICLE IV

DUTY OF OFFICERS

The duties of the President, Vice-President, Secretary, and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of TRANSACTIONS.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

ARTICLE V

COUNCIL

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

ARTICLE VI

MEETINGS

1. The Association shall hold an annual meeting either in the City of Washington, D. C., or at Atlantic City at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology, and miscellaneous business.

4. The President shall have complete charge of, and responsibility for, the program. He shall have power to accept or reject any paper offered. He shall have power to limit the number of papers, and to assign a time limit for each one. Papers shall be presented to the Association only in abstract, and preferably shall not be read from manuscript. They may be published in full in the TRANSACTIONS as also in any other medical publication.

5. Each member or guest having a paper on the program is under obligation to furnish a copy of his paper or a sufficient abstract thereof to the Recorder for publication in the TRANSACTIONS. The time limit for the receipt of manuscript and for the closure of the *Transactions* to further additions shall be fixed by the Council.

6. The referee, co-referee, and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

ARTICLE VII

QUORUM

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, twenty-five shall be necessary for a quorum, and for altering the Constitution fifty members shall be necessary.

ARTICLE VIII

ELECTION OF MEMBERS

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

ARTICLE IX

ANNUAL DUES

The annual dues of the Association shall be such as the Council from time to time may fix, from the payment of which honorary and emeritus members shall be exempt.

ARTICLE X

AMENDMENTS TO THE CONSTITUTION

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendment; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present.

MINUTES

OF THE

THIRTY-EIGHTH ANNUAL MEETING

Held at the Hotel Traymore, Atlantic City, N. J., May 1 and 2, 1923.

The following members were present at the meeting:

Abbott, A. C.
Abel, J. J.
Adams, S. S.
Allen, F. M.
Amoss, H. L.
Anderson, J. F.
Auer, J.
Austin, J. H.
Barker, L. F.
Bass, C. C.
Blake, F. G.
Blankenhorn, M. A.
Blumer, G.
Boggs, T. R.
Brill, N. E.
Brooks, H.
Brown, L.
Brown, T. R.
Brown, W. H.
Bunting, C. H.
Camac, C. N. B.
Carter, E. P.
Cecil, R.
Chesney, A. M.
Christian, H. A.
Cohen, S. S.
Cohn, A. E.
Cole, R. I.
Coleman, W.
Collins, J.
Conner, L. A.
Coplin, W. M. L.
Dick, G. F.
Draper, G.
Drinker, C. K.
DuBois, E. F.
Edmunds, C. W.
Emerson, H.
Evans, J. S.
Eyster, J. H.
Fitz, R.
Flexner, S.
Ford, W. W.
Foster, N. B.
Friedenwald, J.
Frothingham, C., Jr.
Fulton, F. T.
Funk, E. H.
Geyelin, H. K.
Giffin, H. Z.
Gordinier, H. C.
Greene, C. L.
Guthrie, C. G.
Gwyn, N. B.
Hamburger, W. W.
Hare, H. A.
Hart, T. S.
Heard, J. D.
Herrick, J. B.
Herrick, W. W.
Hess, A. F.
Hewlett, A. W.
Howard, C. P.
Howland, J.
Hunt, J. R.
Irons, E. E.
Jackson, H.
Jobling, J. W.
Joslin, E. P.
Karsner, H. T.
Koplik, H.
Krumbhaar, E. B.
Lambert, S. W.
Lee, R. I.
Lewis, M. J.
Libman, E.
Locke, E. A.
Longcope, W. T.
Lord, F. T.
McCrae, T.
McLester, J. S.
MacCallum, W. G.
Marriott, W. M.
Martin, C. F.
Means, J. H.
Meyer, A.
Miller, J. A.
Miller, J. L.
Minot, G. R.
Morris, R. S.

Mosenthal, H. O.
Moss, W. L.
Murphy, J. B.
Musser, J. H., Jr.
Newburgh, L. N.
Noguchi, H.
Norris, G. W.
Ordway, T.
Palmer, W. W.
Peabody, F. W.
Pepper, O. H. P.
Piersol, G. M.
Plumer, H. S.
Pratt, J. H.
Rehfuss, M. E.
Riesman, D.
Robinson, G. C.
Rous, P.
Sailer, J.
Scott, R. W.
Sewall, H.
Sippy, B. W.
Steiner, W. R.
Stengel, A.
Stockton, C. G.
Swift, H. F.
Taussig, A. E.
Thayer, W. S.
Vanderhoof, D.
Wadsworth, A. B.
Warfield, L. M.
Warthin, A. S.
Webb, G. B.
Whipple, G. H.
White, F. W.
White, P. D.
White, W. C.
Wilson, L. B.
Woodyatt, R. T.
Zinsser, H.

Tuesday Morning, May 1

The Association was called to order by President Herrick, who delivered the President's address.

The Treasurer's report was presented by Dr. McCrae. It showed receipts of $2791.36 and expenditures of $2764.23, leaving a balance of $27.13. The President appointed Drs. Irons and Cohn as auditors.

The Secretary presented the report of the Council with the following recommendations:

1. That the dues for the coming year be $15 for Active Members in active practice; $7.50 for Associate Members, and $5 for those in whole-time positions.

2. That the next meeting be held in Atlantic City on May 6 and 7, 1924.

3. That the following at their own request be transferred to the Emeritus List: Drs. H. M. Biggs, F. Billings, R. C. Cabot, G. Dock, M. W. Richardson, and F. F. Russell.

4. That the election of those nominated for Corresponding Membership be recommended.

The program was then proceeded with:

Dr. Warren Coleman presented a paper on "The Prevention of Certain forms of Chronic Cardiac Valvular Disease," which was discussed by Drs. H. Brooks, H. Koplik and W. S. Thayer.

Dr. C. F. Martin presented a paper on "Myocardial Lesions," which was discussed by Dr. L. F. Barker.

Dr. A. S. Warthin presented a paper on "Diphtheria Myocarditis," which was discussed by Drs. C. H. Bunting, H. Christian and Dr. Wenckebach, and the discussion closed by Dr. Warthin.

Dr. Walter W. Hamburger and Dr. Walter S. Priest, Jr., presented a paper on "Structural and Functional Involvement of the Heart following Acute Respiratory and Other Acute Infections," which was discussed by Dr. E. B. Krumbhaar and Dr. Wenckebach, and the discussion closed by Dr. Hamburger.

Dr. E. Libman and Dr. Benjamin Sacks presented a paper "Concerning an Atypical Form of Verrucous Endocarditis," which was discussed by Drs. G. Blumer, L. A. Conner and L. F. Barker, and the discussion closed by Dr. Libman.

Dr. A. J. Beams presented a paper on "Arteriovenous Aneurysm," on which there was no discussion.

Dr. J. A. E. Eyster presented a paper on "The Use of the Roentgen Ray in the Diagnosis of Chronic Valvular Heart Disease," which was discussed by Drs. J. H. Pratt, Wenckebach, W. S. Thayer and H. Sewall, and the discussion closed by Dr. Eyster.

Dr. Roger S. Morris and Dr. Carl F. Little presented a paper on "The Physical Findings in Pericarditis with Effusion," which was discussed by Drs. E. Libman, L. A. Conner, W. S. Thayer, W. Coleman and F. T. Lord, and the discussion closed by Dr. Morris.

Dr. W. M. Boothby presented a paper on "The Heart in Exophthalmic Goiter and in Adenomatous Goiter with Hyperthyroidism," which was discussed by Drs. E. B. Krumbhaar, George Norris and the discussion closed by Dr. Willius.

Tuesday Afternoon, May 1

Dr. C. P. Howard presented a paper on "Syphilis of the Lung with Report of Cases," which was discussed by Drs. F. T. Lord, W. S. Thayer, E. H. Funk, G. B. Webb, B. W. Sippy and J. Collins, and the discussion closed by Dr. Howard.

Dr. Alexander McPhedran and Dr. F. G. Banting presented a paper on "Insulin in the Treatment of Severe Diabetes;" Dr. E. P. Joslin presented a paper on "Insulin in the Routine Treatment of Diabetes;" Dr. Rollin T. Woodyatt presented a paper on "Insulin in the Surgical Complications of Diabetes;" Dr. Nellis B. Foster presented a paper on "Insulin in Diabetic Coma;" Dr. H. Rawle Geyelin presented a paper on "Insulin in Diabetes in Children;" and Dr. Frederick M. Allen presented a paper on "Experiments with Insulin," which were discussed jointly by Drs. R. Fitz, A. Stengel, E. P. Joslin, N. B. Foster and H. R. Geyelin, and the discussion closed by Dr. Banting.

Dr. W. W. Herrick presented a paper on "Clinical Observations on Hyperglycemia and Hypertension," which was discussed by Drs. H. O. Mosenthal, W. S. Thayer and S. S. Cohen.

Tuesday Evening, May 1

Dr. Gerald B. Webb and Dr. J. A. Sevier presented a paper on "The Diaphragm Excursion and the Mediastinum in Lateral Recumbent Posture," which was discussed by Dr. F. T. Lord and the discussion closed by Dr. Webb.

Dr. S. Solis Cohen presented a paper on "A Study of Acute Leukemia."

Dr. E. B. Krumbhaar presented a paper on "The Hemolytopoietic System, with a Note on the Value of Splenectomy," which was discussed by Drs. A. S. Warthin and G. B. Webb, and the discussion by Dr. E. B. Krumbhaar.

Dr. Norman B. Gwyn presented a paper on "The Clinical Side of the Condition Spoken of as Massive Collapse of the Lung," which was discussed by Dr. F. T. Lord and the discussion closed by Dr. Gwyn.

Dr. James A. Miller and Dr. Adrian V. S. Lambert presented a paper on "Abscess of the Lung," which was discussed by Drs. C. P. Howard, T. McCrae and F. T. Lord, and the discussion closed by Dr. Miller.

Dr. S. Burt Wolbach and Dr. Channing Frothingham presented a paper on "The Pathological Lesions in the Various Organs Occurring in Epidemic Influenza," which was discussed by Dr. W. G. MacCallum and the discussion closed by Dr. Frothingham.

Dr. Alfred F. Hess presented a paper on "The Therapeutic Effect of Visible and Ultraviolet Rays of Various Wave Lengths," which was discussed by Dr. H. Emerson.

Wednesday Morning, May 2

The following Officers and New Members were elected:

President—C. F. Martin.

Vice-President—L. A. Conner.

Secretary—T. McCrae.

Recorder—T. R. Boggs.

Treasurer—J. A. Capps.

Councillor—F. W. Peabody.

Representative on the Executive of the Congress—G. C. Robinson.

Alternate Representative—R. T. Woodyatt.

Active Members—H. L. Amoss, Baltimore; D. Graham, Toronto; W. Herrick, New York; A. Lambert, New York; C. Minor, Asheville; J. B. Murphy, New York; W. L. Niles, New York; A. N. Richards, Philadelphia; S. Strouse, Chicago; P. D. White, Boston.

Associate Members—A. L. Bloomfield, Baltimore; N. M. Keith, Rochester; W. W. G. MacLachlan, Pittsburgh; E. H. Mason, Mon-

treal; B. S. Oppenheimer, New York; J. E. Paullin, Atlanta; F. N. Wilson, Ann Arbor.

Corresponding Members—Sir H. D. Rolleston, London; Prof. T. R. Elliott, London; Prof. A. Chauffard, Paris; Prof. F. Widal, Paris.

The Auditors reported that the Treasurer's accounts had been audited and found correct.

Dr. George Blumer presented a paper on "Infectious Jaundice in the United States," which was discussed by Drs. J. L. Miller, N. E. Brill, H. Noguchi, W. W. Ford, N. Gwyn and H. Koplik, and the discussion closed by Dr. Blumer.

Dr. Simon Flexner presented a paper on the "Pathogenesis of Epidemic Encephalitis," which was discussed by Drs. H. Zinsser and E. Libman.

Dr. C. W. Edmunds and Dr. Putnam C. Long presented a "Contribution to the Pathological Physiology of Botulism."

Dr. William W. Ford presented a paper on "A New Classification of Mycetismus, or Mushroom Poisoning."

Dr. M. A. Blankenhorn presented a paper on "Chylous and Chyliform Ascites."

Dr. John J. Abel and Dr. C. A. Rouiller presented a paper on "An Exceedingly Powerful Oxytocic and Pressor Substance Obtained from the Posterior Lobe of the Pituitary Gland," which was discussed by Dr. J. L. Miller and the discussion closed by Dr. Abel.

Dr. N. E. Brill and Dr. N. Rosenthal presented a paper on "The Remedial Efficacy of Splenectomy in Chronic Thrombocytopenic Purpura Hemorrhagica," which was discussed by Drs. H. Z. Giffin, G. R. Minot and E. B. Krumbhaar, and the discussion closed by Dr. Brill.

Dr. Joseph Collins and Dr. Hideyo Noguchi presented a paper on "An Experimental Study of Multiple Sclerosis: I. Clinical History and General Discussion; II. Experimental Results in Animals with Blood and Cerebrospinal Fluid," which was discussed by Dr. H. L. Amoss and the discussion closed by Dr. Noguchi.

Wednesday Afternoon, May 2

Dr. Douglas Vanderhoof presented a paper on "The Etiological Relation of Achylia Gastrica to Combined Spinal Sclerosis," which was discussed by Drs. W. S. Thayer, B. W. Sippy and H. S. Plummer, and the discussion closed by Dr. Vanderhoof.

Dr. John Auer presented a paper on "A Study of the Reflexes Arising in the Integument Causing Sensory and Motor Disturbances in Normal Animals; a Contribution to Brown-Séquard's Epilepsy."

Dr. George R. Minot and Dr. Thomas E. Buckman presented a paper on "Certain Aspects of Polycythemia."

Dr. Wade H. Brown, Dr. Louise Pearce and Dr. C. M. Van Allen presented a paper on the "Effects of Operative Interference with the Endocrines on the Growth and Malignancy of a Transplanted Tumor of the Rabbit," which was discussed by Dr. H. Sewall, and the discussion closed by Dr. Brown.

Dr. Blake Donaldson presented a paper on "A Clinical Study of Digitalis Toxemia," which was discussed by Drs. H. Brooks and H. A. Hare, and the discussion closed by Dr. Donaldson.

The following papers were read by title: "A study of Fatal Cases of Bacterial Endocarditis," by Dr. W. S. Thayer; "Some Less Frequently Considered Portals of Entry of Chronic Infections," by Dr. Ernest E. Irons; "A Further Consideration of the Clinical Manifestations of Sprue," by Dr. E. J. Wood; "The Use of Radium Radiations in the Treatment of Tonsils," by Dr. Francis H. Williams; "The Classification of Heart Pain," by Dr. Paul White and Dr. J. Edwin Wood; "Investigations Concerning Immunity in Yaws," by Dr. A. W. Sellards and Dr. E. P. Goodpasture; "A Clinical Study of Some Antirheumatic Drugs," by Dr. Homer F. Swift, Dr. Ralph H. Boots and Dr. C. Philip Miller, Jr.; "Immunity Studies on Rocky Mountain Spotted Fever: II. Prophylactic Inoculation Against Rocky Mountain Spotted Fever," by Dr. Hideyo Noguchi; "Diffuse Epithelioma of the Ependyma of Both Lateral Ventricles," by Dr. L. M. Warfield; "Phyto-pharmacology, with Especial Reference to Some Clinical Applications," by Dr. David J. Macht; "Maternal and Infant Mortality in Physicians' Families," by Dr. Haven Emerson; "The Thrombi of Certain Anaphylactoid Phenomena," by Dr. H. T. Karsner and Dr. P. J. Hanzlik; "Changes in Blood Concentration in Water Intoxication," by Dr. L. G. Rowntree and Dr. C. H. Greene; "Some Observations on the Phenoltetrachlorphthalein Test as a Means of Determining Liver Function," by Dr. Julius Friedenwald and Dr. W. Horsley Gantt; "On the Dilatation of Capillaries and Other Physiological Reactions Produced in Unanesthetized Dogs by Witte's Peptone, Purified Albumoses and Histamine," by Dr. John J. Abel, Dr. E. M. K. Geiling and Dr. A. C. Kolls; "Pyelitis in a Baby Two Weeks Old," by Dr. B. K. Rachford, and "The Vasomotor Element in the Treatment of Cardiovascular Disease," by Dr. Charles P. Emerson.

A unanimous vote of thanks was extended to Dr. Herrick for the interesting program.

THOMAS MCCRAE,
Secretary.

THE PRESIDENT'S ADDRESS

THE RELATION OF THE ASSOCIATION TO THERAPEUTICS

By JAMES B. HERRICK, M.D.
CHICAGO, ILL.

In the last year the Association has lost by death four members, all from the Emeritus list: Dr. George B. Shattuck, of Boston, and Dr. Robert T. Edes, of Reading, Mass., were charter members of 1886; Dr. H. E. Ernst, of Boston, joined in 1888, and Dr. J. S. Thacher, of New York, in 1899. To the present generation these are little more than names. Some of the older members, however, will recall these men as congenial colleagues whose contributions, the result of scholarly training and of keen observation and practical experience in the laboratory and at the bedside, were factors of no small importance in making successful and productive the work of this Association in its earlier years.

According to precedent, only rarely violated, the address of your presiding officer should be brief. I shall adhere to custom. Aside from thanking you for the honor conferred upon me by electing me to this office, I shall invite your attention for only a few moments to one thought.

Last summer I was asked to send a representative of the Association to the meeting of the American Pharmaceutical Association. I wrote a well-known member of this body, who agreed to go as our representative, though later he was unable to do so. In his letter to me concerning the matter, he hinted that very few members of

the Association were interested in these questions of drugs and therapeutics, and tacitly I agreed with him. Then I began to wonder if the pharmacologist was right and that we ought to be interested. Finally, I concluded we were all wrong, that the Association always has been and now is seriously concerned with scientific therapy though not with the drug business. In fact, at the very time that I was regretting we were not interested I was trying to arrange the symposium on insulin treatment of diabetes, feeling that it was a topic that would appeal to all our members. I decided to see what had been our record in the past in this respect, and looked over the thirty-seven volumes of the *Transactions* and found that some of the best minds of this body had presented papers, some of them pioneer papers, on drugs and therapy.

The first article in our *Transactions*, the volume of 1886, is the classic paper by Fitz on the "Pathology of Appendicitis and its Medical *versus* its Surgical Treatment." I found several papers on typhoid fever, including treatment by cold baths and protective inoculation. The use of diphtheria antitoxin has been many times taken up. Thyroid therapy in myxedema, thyroxin, epinephrin and lately insulin have been considered, as has tuberculin. There have been papers on the treatment of pneumonia, the use of vaccines and various sera. Salvarsan has been discussed. Indiscriminate oöphorectomy has been condemned. The therapeutic value of the *x*-ray and of splenectomy has been presented and the management of duodenal ulcer by diet, operation or other means has been set forth. The treatment of tuberculosis and of diabetes has been given due consideration. All these and other kindred topics have been written about and considered in the discussions. With few exceptions they have been handled in ways that subsequently have been shown to have been rational, judicial and scientific. Very rarely have decisions been reached that were based solely on personal impressions—never, I believe, on the laudatory comments of a drug house.

There have been strange waves of therapeutic enthusiasm if the number of papers is to be taken as an index. Thus from 1886 to 1898 there was an average of about five papers a year on therapeutic topics. 1899 to 1905 were barren years, only two a year. In

1901, for instance, there were fifty-six papers offered, only two on Therapy—one by Dr. F. H. Williams on "X-ray in the Treatment of Cancer" and one by Dr. J. J. Putnam on the "Treatment of Epilepsy by Operation." Then the upward curve began. In 1912, eight papers; 1913, twelve; 1914, ten; 1915, fourteen; 1916, eleven, etc.

With a record like this it was unjust to accuse ourselves of lack of interest in therapeutics. The reason for the wrong impression arises, I surmise, because the members, as a class, are primarily but little concerned with drugs and their free use in treatment. We have not rushed into print to herald our experience with every new preparation that has been put on the market. Is this position not correct? Should we not continue to take a stand, if not actively at least negatively, against the tendency still frightfully prevalent to employ drugs in treatment needlessly or even harmlessly? It might be wise to send a representative, if again asked, to let our sentiments be known. Such influence might be for good.

While I was thinking over this matter last year I ran across an article by Strümpell in the *Deutsche medizinishe Wochenschrift* for January 5, 1922. If I had a little more courage I should be tempted to lift this article in its entirety and read it as my address. As it is, I embody many of his ideas in what immediately follows. The article seems to me remarkably sane and timely. It is written by one whose scientific slant is controlled by the cold facts of clinical experience. It is so full of a benevolent philsophy that sometimes comes to the serene old age of him whose mind is every young that, written in a clear and charming style with a touch of gentle humor, with many pointed epigrams but with no rancorous ill-will, it seems to me a gem.

Strümpell, after showing the advances in therapeutics due to surgery, the cold bath and antipyretic handling of fever, the use of sera as in diphtheria, of physiotherapeutic agents, organotherapy, suggestive and psychotherapy, says there are four groups into which therapeutic measures may be divided, the basis of the divisions being the effect on the patient:

1. The necessary or indispensable.
2. The useful.

3. The unnecessary.
4. The harmful.

The necessary measures, *e. g.*, quinine in malaria, antitoxin in diphtheria, thyroid extract in myxedema, are endorsed by all types of physicians. Here would be included, by many, salvarsan, mercury and iodides in syphilis.

The useful, too, meet with no protest: *X*-ray in chronic leukemia; certain diuretics, hypnotics, narcotics and laxatives; special dietetic measures; and some forms of physical and psychic therapy.

But the deplorable fact in Germany is that unnecessary therapy is rampant and on the increase, and this tends to go over into that which is immediately or indirectly harmful. The unnecessary therapy, Strümpell declares, distinctly exceeds in amount the necessary and useful. Is this not true today in our country?

The reasons are the urge of the manufacturers, with their insidious advertising; the urge of the patient, who insists that something be done rather than wait the natural termination of an illness; the urge on the part of the doctor himself, who yields to the desire for credit for the cure and the pecuniary reward that follows. The motto of the quack, "No cure, no pay," has become changed, and, using cure in its German sense of treatment, we may say, "The more cure, the more pay."

If, Strümpell continues, this medical polypragmatism, which is so characterisitic of the present, had as its only results the comforting and satisfying of anxious patients or the increase of income of the physician there might not be strong objection. Let the doctor who has the talent for discovering and exploiting the foolishness of others be permitted to do so—"Mundus vult decipi." The well-to-do man may be permitted the luxury of his foolishness and the gratification of all his wishes so far as it pleases him. But the unscrupulous exploitation of the less well-to-do, more ignorant man, less capable as to judgment and more superstitious, is morally wrong, most deplorable, and should be combated by all honorable physicians.

More than this, the growth of this tendency will ultimately destroy the incentive to the study and the wise application of scientific therapeutics. Harmful therapy is practised by the ignorant,

the careless or the overenthusiastic. The complaisance with which poorly informed men prescribe modern powerful synthetic drugs or inject sera or vaccines of whose action they have no accurate knowledge, would be laughable if it were not so tragic. A child with a dynamite bomb or a moron with an automatic revolver in his hand in a crowded street is not more dangerous.

My conclusion is that this Association has stood, is standing, and should continue to stand for what is best in therapy. A healthy skepticism as to drugs and treatment prevails among its membership. This is fortunate. This skeptical attitude, should remain, but it is to be remembered that an overskeptical mind is as undesired as an overcredulous one. Undue skepticism kills the enthusiastic curiosity of the investigator through whose work progress is to come, be the investigator a worker in the laboratory or at the bedside. An overskeptical, nihilistic, do-nothing attitude on the part of the practitioner is a most fruitful cause of the development among the unscrupulous and ignorant of our profession and the laity of polypharmacy, medical polypragmatism, misguided medical cults and charlatanism.

THE DIAGNOSIS AND PATHOLOGICAL PHYSIOLOGY OF ARTERIOVENOUS ANEURYSM[1]

By C. F. HOOVER, M.D.
AND
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When the systemic arteriovenous circulation is short-circuited by a fistulous communication of sufficient size, there develop symptoms so closely simulating those of myocardial decompensation that it may be very difficult to evaluate the part contributed to the circulatory defect by the arteriovenous communication. In fact, the increased burden on the heart due to short-circuiting the flow of blood may in time produce genuine myocardial decompensation, and the difficulties of diagnosis are still further complicated by the need of determining whether the arteriovenous communciation is the sole cause of circulatory symptoms or only a contributory factor in the presence of cardiac disease. Obviously if all the symptoms are due to arteriovenous fistula, the proper treatment is to close the opening. If the fistula is only a factor of minor importance, the operative procedure may be contraindicated. In the first case we have to report the cardiac symptoms were so pronounced that a large number of physicians and surgeons advised against surgical procedure, believing the arteriovenous fistula to be of minor importance and the cardiac disease to be the chief cause of existing venous stasis, chylous ascites and edema.

We find nowhere in medical literature a discussion of the hydraulics of arterial bloodflow in arteriovenous fistula, nor any attempt to differentiate between cardiac enlargement caused by arteriovenous

[1] From the Medical Department, Western Reserve School of Medicine, Lakeside Hospital, Cleveland, Ohio.

openings and that caused by primary disease of the myocardium. These questions must be unequivocally answered before a patient can be given sound advice on the question of operation. When the fistula is in a location that is under digital control, as in fistula between the femoral artery and vein, it is a perfectly simple matter to compress the artery and determine how the hydraulics of the circulation are affected by eliminating the fistula from the circulation. When, however, the fistula is beyond manual control, as in the root of the neck or intrathoracic or intra-abdominal, then the problem of diagnosis becomes much more difficult.

We shall in this communication first describe 2 patients with arteriovenous fistula in the femoral vessels. In one patient the leak could be readily shunted out by compression of the femoral artery at Poupart's ligament, but in the other case the patient had so much edema and so much pain that he could not tolerate digital pressure on the femoral vessels, nor would he tolerate a ligature about the thigh. This was probably the reason so many physicians had failed to evaluate the fistula in this man's circulatory symptoms.

Case I.—The patient was a young man, aged thirty-two years, who was admitted to Lakeside Hospital on November 29, 1920. Two years and two months before, while serving in a mortar battery with the army in France, he had received a rifle bullet through the right thigh at the lower end of Hunter's canal. From the patient's history it seems he had no fever or any evidence of infection of his wound. About two weeks before he got out of bed, which was about two and a half months after receiving the wound, he observed that his right thigh and leg were swollen and decidedly larger than the left. When walking on crutches, he stepped on the right foot of the wounded side and held his left foot off the ground on account of a superficial wound in the left knee, received at the same time as the wound in the right thigh. He observed that he was very short of breath and began to have signs of fulness in the abdomen. He was then put to bed again, and on examination was found to have free fluid in the belly cavity. Two weeks later his abdomen was tapped to relieve the ascitic accumulation. Within the following two years the abdomen was tapped forty times for the relief of ascites.

When this patient came to the hospital he was able to walk by the aid of one crutch and a cane. The abdomen was greatly distended, and his thorax, extremities and face were emaciated. The patient seemed to suffer more from exhaustion than from air hunger. Although his ability to get

about was very limited, he did not cough or exhibit the symptoms of a patient suffering from a high degree of stasis in the pulmonary circulation. Physical examination showed the apex of the heart at the fifth intercostal space, two-thirds of the way to the anterior axillary line from the left mid-clavicular line. The impulse of the right ventricle was strong, and there were a distinct systolic impulse and a diastolic impact over the conus arteriosus. There was not a clear differentiation between the areas of impulse, but the left ventricular impulse could be differentiated from the right. The precordial area of dulness did not extend beyond the right border of the sternum in the third and fourth interspaces. During inspiration the inner half of the left costal margin was diminished in its laterad movement, but the inner portion of the right costal margin moved readily away from the median line. The outer parts of both costal margins moved symmetrically outward during inspiration. The external and internal jugular veins were distended and under considerable pressure. When he was lying with his hands at his side a distinct centrifugal pulse was visible in the veins of the hands, and the right hand had to be lifted at least 12 inches above the level of the heart before the veins collapsed. The liver was plainly palpable four fingers' breadth below the costal margin in the right nipple-line. There was a strong systolic pulsation of the liver, which was synchronous with the pulse in the carotid artery, and it was so strong that after the ascitic fluid was removed the pulsation of the liver caused a lateral thrust of the ribs on the right side that dragged the entire thorax to the right. With each cardiac systole the lower right ribs were thrust so far in a lateral direction that the borders of the left ribs were drawn toward the right. The femoral vein on the right side was greatly distended and the same kind of systolic pulse was visible as in the jugular veins, bulbus venosus and liver. At the lower end of Hunter's canal there was a strong thrill, which was palpable from that position as far upward as Poupart's ligament. Over this entire distance there was a loud systolic murmur, but below the origin of the thrill on the right side there was no murmur audible and no palpebral thrill. The pulse in the dorsalis pedis artery was not palpable on either foot, but the posterior tibial pulse on both sides was distinctly palpable. The right thigh and leg were very edematous, and there was also slight edema of the left leg and ankle.

A six-foot roentgenogram of the heart showed a globular enlargement. The contour revealed an enlargement of the right ventricle as well as of the left, but showed no evidences of distention of the right auricle to the right of the sternum. When synchronous tracings of the pulse in the bulbus venosus and in the femoral vein of the right side were taken, there was no evidence of an auricular pulse. The pulse was purely systolic in time and the jugular pulse preceded that of the femoral by $\frac{1}{10}$ second, so that so far as pulsation of the liver, jugular vein and femoral vein were concerned one would be compelled to believe this man had a tricuspid

insufficiency and that the venous pulsations might be cardiac in origin or might originate from the arteriovenous opening. There were several reasons, however, for believing that the cardiac involvement was secondary to the arteriovenous fistula, and that all the venous phenomena originated from the direct arterial communication and not from cardiac decompensation.

The first of these reasons was the want of enlargement of the right auricle. If the venous phenomena at the bulbus venosus and in the liver were secondary to tricuspid insufficiency there must be an enlarged right auricle, and, therefore, the fact that there was no evidence of flattening of the subcardial diaphragm at the right of the median line gave rise to the suspicion that the right auricle was not enlarged. Percussion, the fluoroscope and the *x*-ray plate all confirmed this finding. Moreover, the contour of the heart indicated that the right and left ventricles were equally involved and that their enlargement was due to a common cause. That it could not be from a decompensated left ventricle was suggested by the fact that the patient had a lung capacity of 2500 cc when his expected vital capacity was not above 3500 cc. Had all the venous stasis been in consequence of a decompensation of the left ventricle, he would certainly have had pronounced lung rigidity with a great reduction in his vital capacity. Under such circumstances we should have expected the vital capacity to be reduced to about 1500 cc or even 1200 cc.

As above stated, the patient would not tolerate sufficient pressure over the region of the femoral artery to shut out the arteriovenous leak. So in anticipation of an operation we could prognosticate only on the basis of our physical examination, but these two points—namely, the want of evidence of stasis in the pulmonary circulation and of ectasis of the right auricle—were sufficient for advising operative procedure. Up to this time surgery had not been advised, because the patient was believed to have a primary cardiac disease; to substantiate this interpretation a positive Wassermann reaction on the blood had finally been procured after four trials, and this test had determined his physicians not to operate but to have the patient treated for syphilitic myocarditis.

December 5, 1920, we removed 11 liters of ascitic fluid by paracentesis. The fluid was milky in appearance and did not clarify by centrifugation. There were only 135 cells per cu. mm., and the amount of albumin, although not quantitatively determined, was certainly smaller than usually found in pure transudates. Although the fluid did not clarify by contact with ether, Dr. Blankenhorn was able to recover fat in considerable amounts by extraction with petroleum ether in a reflux condenser, and further studies of this fluid, reported elsewhere by Dr. Blankenhorn, proved its turbidity to be caused by fat in a finely divided emulsion. On the day after the ascitic fluid was removed the patient was operated and there was no reaccumulation.

December 6, 1920, Dr. Crile operated on the patient under local anesthesia with nitrous oxide in small amounts. The patient was conscious during most of the operation. The vein and artery at the site of the communication were freely opened. On the inner surface of the artery, in an area of 4 by 2 cm., there were about ten small sinuses plainly visible. The collected area of the lumina of all these sinuses, which presented a sieve-like appearance, was not in excess of the cross-section of the artery. This sieve-like area was not removed but was separated from the neighboring structures by deep ligatures on all four sides.

Directly after the operation it was quite apparent that there had been no primary heart disease and that all the circulatory symptoms had been caused by the arteriovenous fistula. The character of the heart impulse was immediately changed. Although the area of precordial dulness was not lessened, the systolic impulse and diastolic impact over the conus arteriosus of the right ventricle were no longer perceptible. Only the apex impulse was palpable. The contact of the cardiac impulse with the anterior chest wall was diminished in its vigor. One gained the impression that the heart was less globular and the right ventricle smaller, although the location of the apex of the left ventricle was unchanged and the right border of the heart was still at the right sternal border. The large veins were no longer distended and the centrifugal systolic venous pulse in the jugular vein was replaced by a presystolic centrifugal wave. The hepatic pulse ceased and the lower border of the liver was slightly below the costal border in the right nipple-line. Its consistency was somewhat in excess of the normal and its edge slightly rounded, not sharp as in hepatic cirrhosis. The impression one got from palpating the liver before and after the operation was that the great engorgement within the hepatic veins was allayed, but that the edema of the liver persisted. However, within a few days after the operation the liver was no longer palpable and its percussion boundaries were quite normal.

There were several preoperative and postoperative observations that were interesting. For instance, before the operation the minute volume-flow through the right foot (the affected side) was 1.16 gm. per 100 cc of foot volume, as measured by Stewart's method, and through the left foot it was 3.0 gm. per 100 cc; but one month after the operation the same method gave an equal volume flow on the two sides, viz., 1.8 gm. per 100 cc of foot volume, which is within the normal limits. Before the operation there was a marked retention of body fluids, only about half the intake of fluids being eliminated by the kidney, although the phthalein kidney test gave a normal result. The urine at this time contained a trace of albumin and a few hyaline and granular casts. After the operation there was no retention of body fluids and the urine became normal. The vital capacity of the lungs also became normal, being increased from 2500 to 3500 cc. This increase in pulmonary extensibility was more apparent than real. It was in all probability

unchanged, for the patient's muscular vigor was so much improved by the closure of the arteriovenous fistula that this alone could account for the apparent increase in lung capacity.

Besides the modification in size of the heart and the disappearance of venous engorgement the most striking and interesting change was in the character of the arterial pulse. Before the operation the pulse was monocrotic and had an extent and celerity in the anacrotus and catacrotus that were suggestive of aortic insufficiency. The arterial pressure measured 115/65. After the operation the pulse had a smaller excursion and the pressure measured 145/95. This was a very striking change in the systolic and diastolic pressure with the pulse pressure unchanged, and as we shall later show it occurs only in arteriovenous fistula. All other cardiovascular diseases that modify arterial pressures alter the pulse pressure.

FIG. 1.—*A*, a teleroentgenogram of the heart of the patient described in Case I before the *A–V* fistula was closed; *B*, the teleroentgenogram made four weeks after the operation.

By the latter part of February, eight weeks after the operation, the patient was discharged in perfect health. The roentgenograms of the heart taken before and after operation show a marked diminution in the size of the heart (Figs. 1, A and B). All the cardiovascular and respiratory signs were perfectly normal. The liver had a normal conformation, size and consistency. The urine was normal and the blood-flow in the feet was the same.

CASE II.—The patient was an Italian woman, aged fifty-eight years, who was admitted to Lakeside Hospital in April, 1921, complaining of shortness of breath and abdominal pain. Four years before entering the hospital the patient was wounded by a rifle bullet in the upper right thigh. She was confined to bed for eighteen days. After recovery from her wound

she noticed a pulsation at the lower end of Scarpa's triangle. A year later there was dyspnea on slight exertion and the ability to exercise grew gradually less. The patient had a well-pronounced cardiovascular disease, as shown by the cardiac enlargement and an arterial pressure of 210/110. In the jugular vein and bulbus venosus there was a systolic centrifugal pulse. The liver was at the level of the umbilicus in the midclavicular line and revealed a pronounced systolic pulse that was synchronous with that in the bulbus venosus. The contour of the heart was globular, although the differentiation between the areas of the left and the right ventricular impulses was more clearly defined than in the first patient. It was noticed, however, that although there was a pronounced hepatic pulse the right boundary of precordial dulness did not extend beyond the right border of the sternum. The subcardial diaphragm was not flattened at the right of the median line but it was depressed at the left, as shown by the inspiratory excursions of the costal borders. The inner half of the left border did not move outward during inspiration, but the outer half moved strongly laterad, as did the entire right costal margin.

There were no evidences of stasis in the pulmonary circulation. Four cm. below Poupart's ligament there was an intense systolic thrill and loud systolic murmur, which was audible during the entire cardiac cycle, but was greatly accentuated with the expulsive phase of the left ventricle. Although the femoral vein was enlarged there was no edema of the thigh or leg of the affected side. When the femoral artery was obliterated at Poupart's ligament by digital compression, there followed some striking alterations in the arterial pressure and character of the pulse. The systolic and diastolic blood pressures both rose 40 mm. Hg, but the pulse pressure remained the same. Before compression of the femoral artery the pressure measured in either arm was 210/110, and during compression it was 250/150. When the arteriovenous leak was eliminated the excursion of the radial and dorsalis pedis arteries was distinctly lessened, as perceived both by touch and by sight. With the arteriovenous leak the pulse excursion had a range and celerity suggestive of insufficiency of the aortic valves or sclerosis of the aorta. When the arteriovenous leak was eliminated, the pulse instantly assumed the character of pulsus durans, which is so marked in the Gull and Sutton variety of arterial sclerosis. The excursion of the artery was lessened and an interruption high in the catacrotus was plainly visible and palpable in the dorsalis pedis, radial and brachial arteries. This alteration was clearly due to elimination of the systolic and diastolic leak from the femoral artery into the femoral vein. The systolic pulse in the jugular vein was replaced by a presystolic centrifugal pulse, which was plainly auricular in origin. The hepatic pulse ceased with elimination of the arteriovenous leak and the size of the liver perceptibly diminished.

These changes in the arterial pulse was plainly shown in a tracing made from the radial artery, as seen in Fig. 2. At *x* the femoral artery above

the fistula was compressed at the end of cardiac diastole. Instantly the tracing rose to the same height as before compression, but the catacrotus descended only one-third as far. The force of the spring that drove the pellote downward so as to register a downward excursion of the needle of 8 mm. now drove the needle downward only 3 mm. This was of course due to the increased filling of the artery and the rise of 40 mm. of mercury in the diastolic pressure. As the sphygmograph registers only the excursion of the arterial wall, with the stiffening of the arterial system, the excurison of the wall is much diminished. At *y* the compressing finger was lifted and instantly the original arterial excursion was resumed. The pulse rate was distinctly increased when the leak was eliminated and not slowed as reported by other observers. The time marker shows no interruption in the tracing.

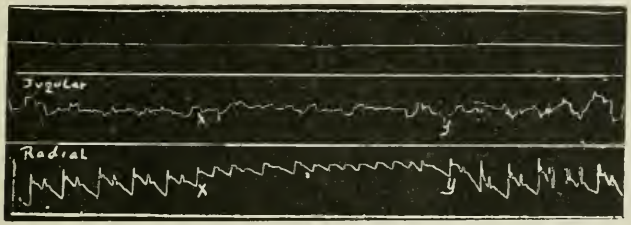

FIG. 2.—In the lower tracing at *x* the femoral artery was compressed and instantly the recording needle rose and recorded from there on the small excursion of the pulses durans in the radial artery. At *v* the compressing finger was lifted and instantly there was a return to the pulse of the celer character. During this manipulation the instrument was not stopped.

An operation was not advised on this patient because she had a severe cardiovascular and renal disease which forbade any promise of restoration to health after closure of the arteriovenous leak. In the second patient the arteriovenous leak was not so large as in the first, but the hydraulics of the blood-flow were affected exactly the same in both though in different degrees. In the second patient the significance of the atertiovenous leak was easily determined by compression of the femoral artery above the fistula.

In these 2 cases there are two demonstrable effects on the circulation that characterize the lesion and also enable the clinician to evaluate the burden added to the heart by the arterial leak. When there is a central leak, *i.e.*, of the aortic valves, the severity of the leak is clinically estimated by enlargement of the left ventricle and increase of the pulse pressure. If the diastolic pressure is lowered there must be a compensatory rise of the systolic pressure to main-

tain a normal minute volume flow of blood. The left ventricle enlarges to accommodate a compensatory diastolic filling of its chamber. The leak, however, under these circumstances, is purely diastolic. If there is a leak distal to the aortic valves there will, of necessity, be an enlargement of all the chambers of the heart if the minute volume-flow of blood is to be maintained. On the central side of the leak there must be an increased volume-flow if the normal flow is maintained in all the distal parts. If 100 cc be the normal output of a left ventricle and an aortic diastolic leak of 20 cc be imposed, then, the rate remaining the same, the systolic output of the ventricle must become 120 cc, but only the left ventricle need enlarge to meet this compensatory measure. If the leak of 20 cc during the entire cardiac cycle occurs distally to the aortic valves, not only will there be required a compensatory dilatation of the left ventricle but the right ventricle will have to meet an equal dilatation, but an equal measure of dilatation on the part of the auricles is, for obvious reasons, not required. The same kind of cardiac enlargement will be needed as occurs in other diseases attended with an increased minute volume-flow through the heart. In acute Graves' disease and severe chlorosis the cavities of the ventricles enlarge, but it is a compensatory enlargement, not a cardiectasis, as in myocardial decompensation, and there is no demonstrable enlargement of the right auricle to the right of the sternum. Let it be understood that enlargement of the precordial area of dulness to the right of the sternum is always due either to ectasis of the right auricle or to an enlarged pericardial sac. The atrioventricular sulcus of the right heart pretty closely follows the right border of the sternum from the third to the fifth intercostal space. When the right ventricle enlarges its base is not dislocated to the right, but its boundaries move upward to the left in the line of the conus arteriosus and laterally to it, and also downward to the left. When there is ectasis of the right ventricle and auricle from myocardial decompensation the subcardial diaphragm to the right of the median line is flattened and the inner half of the right costal margin is restrained in its lateral movement during inspiration, and in severe cases it may be drawn mediad. When, however, the cardiac enlargement is compensatory for an increased volume-flow of blood, as occurs in

Graves' disease or in arteriovenous fistula, the subcardial diaphragm is not flattened; the heart seems to be erect, and although enlarged it does not encroach on the phrenic arch.

The want of enlargement of the right auricle is the most important sign in arteriovenous fistula when the volume of the leak is sufficient to cause a systolic liver pulse, for when hepatic pulse is due to cardiac decompensation the subcardial diaphragm at the right of the median line is flattened so that the inner half of the right costal border is either restrained in its laterad movement or drawn toward the median line in inspiration. This sign is the key to differential diagnosis when the leak is not under command of the fingers, for a globular enlargement of the heart, attended with a systolic centrifugal pulse in the veins and a strong hepatic pulse is very likely to be unquestioningly disposed of as venous stasis from cardiac decompensation. When the arteriovenous fistula is under digital command it is an obvious and simple procedure to demonstrate the degree of arterial leak. If elimination of the leak does not modify the systolic and diastolic pressure, then the arteriovenous fistula can have no significance for the systemic circulation. The change in blood pressure without change in the pulse pressure occurs only in this affection. All other sources for changes in blood pressure alter the pulse pressure. This is true in diseases of the aortic valve and also when the output of the heart is increased or diminished if the peripheral resistance changes or remains the same.

Should a patient have arterial hypertonus with a pressure of 250/150 and the vasomotor tone be relaxed so that the systolic pressure is lowered to 210 the diastolic pressure will not be lowered an equal amount. The diastolic pressure may drop to 125 or to 120, but it will not come down to 110, as occurred in our second patient when the arterivenous leak was reopened after it had been eliminated by digital compression.

Pathological Physiology of Arteriovenous Fistula. There were several considerations in these cases of arteriovenous fistula that demanded experimental confirmation and further clarification. The essential points we wished to study were: The changes in arterial pressure without change of pulse pressure; enlargement of both ventricles without ectasis of the auricles; and hepatic pulsation.

We soon found that anastomoses between normal vessels and fistulæ between arteries and veins resulting from trauma gave very different results. In neither of our two patients with femoral arteriovenous fistula could the leak have exceeded that of the cross-section of a femoral artery, but the arterial and venous pressures were much more affected in our patients than in our experimental animals even when the proportionate arteriovenous anastomoses implicated a larger vascular lumen. In the first of our two patients, it will be remembered, the arterial pressure was 115/65 before and 145/95 after the leak was closed; and in the second patient it was 210/110 before and 250/150 afterward. The soldier had a much larger leak than the woman, although his arterial pressure was raised 10 mm. Hg less. The woman had severe arterial sclerosis, so that the stoppage of her smaller leak raised the pressure more than did the stoppage of the larger one in the man.

To reproduce these results in animals we anastomosed both carotid arteries of a dog with their adjacent external jugular veins, with the expectation that the consequent arteriovenous leak would proportionately equal or exceed that of our patients. With the aid of our surgical colleague, Dr. Frank Gibson, such anastomoses were made in May, 1922. By the middle of the following November the dog showed no signs of venous stasis, and *x*-ray plates of the dog's heart made each month showed no appreciable alteration in the size of the heart. The dog was killed after the interval of six months and the arteriovenous communications were perfectly clear, without obstructing thrombi in either vein or artery, and had a circumference of 7 mm. on each side. During life there were a strongly palpable thrill and a loud murmur over each opening, and if the lumina of the cut ends of the carotids had not been greatly diminished by vasomotor constriction the circulatory changes seen in our first patient would certainly have been reproduced, as the dog's arteriovenous communication at autopsy was proportionately much larger than our patient could possibly have had. We sought to remedy this constriction in the dog by dissecting off the adventitiæ from the anastomosed arteries, but the thrombi in the veins at the points of anastomosis defeated the purpose of the experiment. When the dog's carotid-jugular anastomoses were freely open the

character of the femoral pulse was perceptibly modified by alternately closing and releasing the carotids, but the palpable changes in the character of the pulse were not nearly so pronounced as in either of the two patients with unilateral fistula in their femoral vessels.

We then tried anastomosing one common carotid artery of a dog with its neighboring external jugular vein, so that the proximal end of the artery opened freely into the vein. An arteriovenous leak as great as in either of the patients above described might have been expected, but the results were disappointing. After the carotid-jugular communication was established the palpable thrill and murmur indicated a large leak, and by palpating the femoral artery while the arteriovenous opening was alternately closed and opened the change in the character of the femoral pulse was plainly perceptible to the palpating finger. When the arteriovenous communication was open the excursion of the femoral artery partook of the celer character, and when it was closed the artery had less excursion. When a cannula connected with a mercury manometer was inserted in the central end of the femoral artery the changes in pressure were found to be considerably less than one would expect from the thrill and murmur and the palpable and visible changes in the femoral arterial pulse. In the accompanying tracing (Fig. 3) the arterial pressures from such an experiment are recorded. Although the femoral artery could plainly be seen to be fuller and its walls more taut when the arteriovenous opening was closed, still the pressure tracings fail to show when the opening was closed or open. The pressure changes were not sufficient to surmount those that occurred with respiration.

This experiment (with the one previously described, in which both carotids and jugulars were united) shows very clearly that when arteriovenous communications are established between vessels with normal walls the results are very different from those that occur in arteriovenous fistula following trauma. In normal vessel walls the vasomotor defense against hemorrhage is operative, whereas in diseased walls the leak is constant and unaffected by vascular constriction. Two arteriovenous communications, each found at autopsy to have a circumference of 7 mm., would in a 12-kilo dog

provide a proportionately much larger leak than a unilateral arteriovenous fistula in the femoral artery of man. In the experimental dog, however, we are dealing with the cut ends of normal arteries which respond with vasomotor constriction as a defense against hemorrhage; but in wounded patients the arteriovenous fistulæ are formed in vascular walls that have lost their unstriped muscular fibers where the fistulæ form.

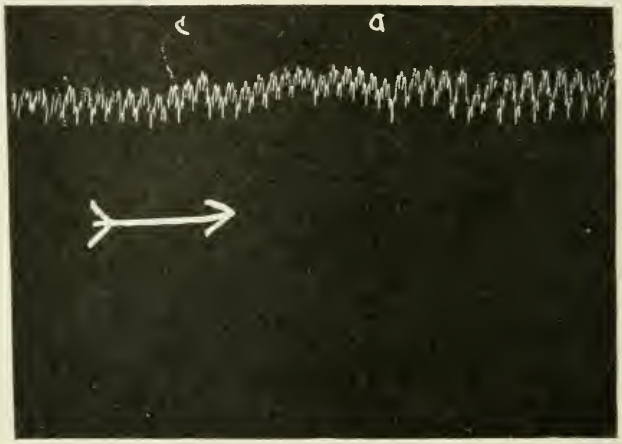

Fig. 3.—This is a tracing from the mercury manometer in the femoral artery of a dog whose carotid artery and jugular vein were anastomosed. At *c* the carotid was closed and at *o* it was opened. Without these indicators one could not tell by the tracing when the *A*–*V* communication was open or shut.

Confusion with Aortic Insufficiency. In several French publications during and since the World War, patients similar to our first one are described as having cardiovascular symptoms like those of insufficiency of the aortic valves. The authors describe the pulse as having a celer character quite like that of aortic insufficiency, and the heart is also described as having the size and contour seen in this valvular defect. According to our observations the size and contour of the heart and pulse differ greatly in the two conditions. The size and contour of the heart will be reserved for later discussion, and for the present we will describe the pulse character and the arterial blood pressure.

Celerity of the pulse as described in the French publications is not celerity in arterial pressure variations but in extent of excursion of the arterial wall. As shown in our experiment in which only one carotid of a dog was connected with the jugular vein, the opening of the arteriovenous communication caused a visibly increased excursion of the exposed femoral artery, but the systolic and diastolic pressures were so little affected that the manometric tracing of the arterial pressure failed to show when the arteriovenous communication was open or closed. By palpation the opening and closure of the arteriovenous communication could be accurately perceived, and still the mercury manometer was not sufficiently delicate to record the variations in pressure. In our second patient, who had arterial sclerosis, closure of the leak changed a pulsus celer into a very pronounced pulsus durans, with a rise of 40 mm. Hg in the maximum arterial pressure; but in spite of this very marked visible and palpable transformation from pulsus celer to pulsus durans the pulse pressure remained the same, as measured by means of the pneumatic cuff on the arm.

With the hope of getting accurate data on the relation between pulse pressure and arteriovenous fistulæ, we employed the Hürthle apparatus designed for the purpose, but our results were equivocal. The nature of the experiment was such that other factors than the A–V communication came into play and the results gave both negatory and confirmatory results as one chose to measure the pulse pressure at selected intervals. In fact, the results were not as satisfactory as got by means of the mercury manometer. So far as our endeavors in the matter go, we are compelled to abide by the results of the pneumatic cuff, which gave the same results not only in our cases but in the cases of four other observers, who report the unchanging pulse pressures, although the fact did not arouse their interest.

Whether the cuff is an absolutely correct method or not for measuring pulse pressure does not affect the value of the clinical observation. The fact remains that, with the best clinical method for the purpose, pulse pressure is found to be unchanged with alterations in maximum pressure in this lesion only. And, furthermore, when closure of an A–V opening does not modify the systolic pressure the lesion is of no serious significance for the circulation.

FIG. 4.—This tracing was made from a mercury manometer connected with a carotid artery of a dog whose abdominal aorta and cava were connected by a U-tube. *c* in each instance marks the point where the aorta-cava communication was closed, and *o* in each instance marks the place where it was opened.

Fig. 4 is a tracing made by a mercury manometer connected with the carotid artery of a dog in which the proximal ends of the cut abdominal aorta and cava were connected by a paraffined U-tube. At the points marked *S* the A–V communication was shut and at *O* it was opened. The tracing shows the systolic pressure much higher and the pulse pressure smaller during the shut periods. There is a difference of 25 mm. Hg between the two periods, but the pulse pressures differ only by 4 mm. Furthermore, during the closed periods the pulse pressure recorded is the smaller, which differs from what happens when arterial pressure is raised by other means. Even by the Hg manometric recording method, as the pressure rises from the use of adrenalin the pulse pressure increases.

Although the mercury manometer does not accurately trace the pulse pressure, it does betray gross changes. This is shown in a carotid pressure tracing in an experiment of the same kind. At *S*, Fig. 5, the A–V communication was closed, at *O* it was open; then at *ad* the drum was stopped and 5 minims of 1 to 1000 adrenalin injected intravenously. With the A–V communication left open the pressure rose from 90 mm. to 130 mm., but the excursion of the manometer changed from 8 mm. to 14 mm. In these pulse pressure changes we see just the reverse of those occurring with opening and closing an A–V communication, as shown by the mercury manometer. Adrenalin raises the blood pressure and enlarges the pulse pressure; closing an A–V opening raises the arterial but does not increase the pulse pressure. While the pulse pressure was enormously increased under the maximum effect of adrenalin at *S* the A–V opening was closed, and at *O* again opened. Of course, here we have two operating factors, one a constant, *i. e.*, the opening and closure of the A–V communication, and the other a variant, *i. e.*, vasomotor pressor effect. But in the periods of *S* and *O*, where the pressor effect seems probably the same, the pulse pressure is little changed at *O* by opening the A–V passage, although the systolic pressure is much lowered by the procedure. Insufficiency of the aortic valves lowers the diastolic pressure and is attended with a compensatory rise in the systolic pressure. In fact, every change in maximum blood pressure that occurs with any disease of the aortic valves or the aorta or peripheral arteries is attended with change in the pulse pressure.

The rise in maximum blood pressure of our second patient when the A–V communication was closed came promptly with the closure.

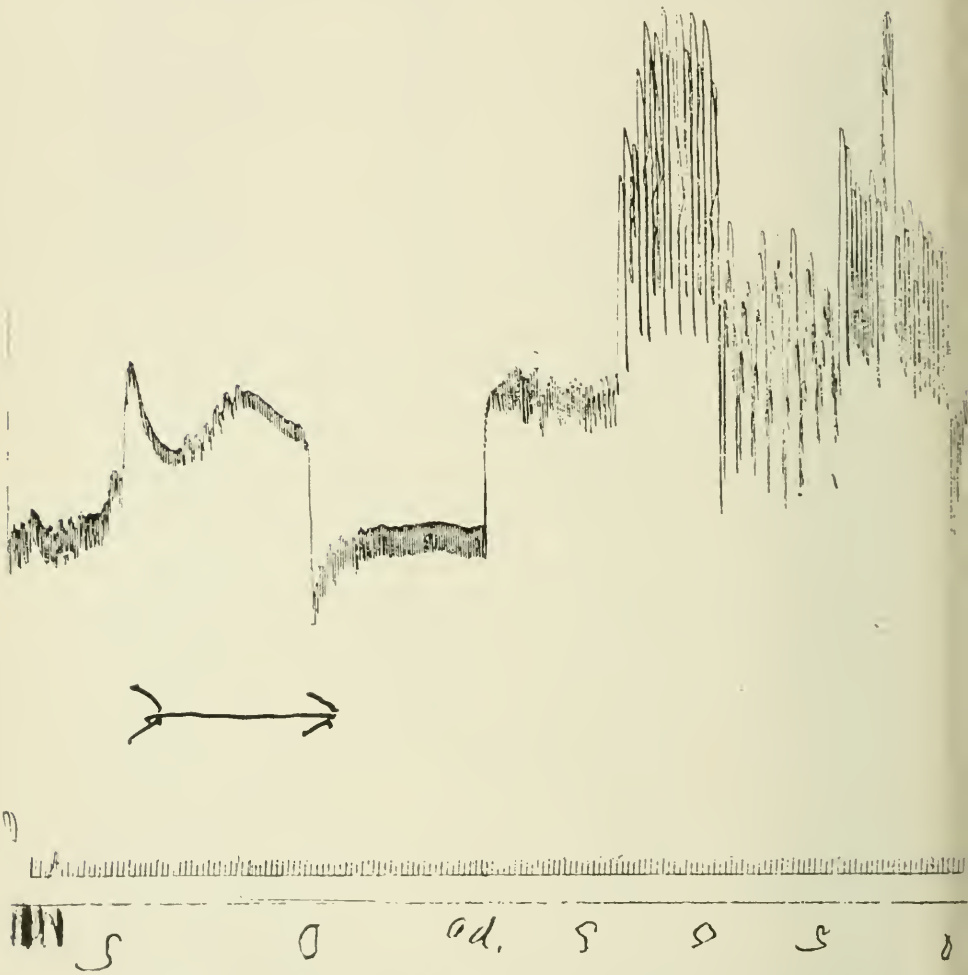

Fig. 5.—A tracing from the carotid artery of a dog operated under the same conditions in which the tracing in Fig. 4 was made. This tracing shows the contrast between the effects on pulse pressures that are produced by closing A–V communications and by increasing peripheral arterial resistance by the use of adrenalin.

When the femoral artery above the fistula was compressed at the end of a cardiac systole, the next arterial pulse apparently had the maximum rise, and this blood pressure and pulse pressure were

maintained until the A–V communication was reopened, when the return to the former arterial and pulse pressure as promptly followed. This change is too prompt to include any vasomotor factor.

The mechanism of an arteriovenous leak differs from that of the central leak (aortic insufficiency) and of the peripheral leak (vasomotor relaxation). In the central leak the mechanism is operative during diastole and not in systole; in the arteriovenous leak and in vasomotor relaxation the mechanism is operative during the entire cardiac cycle, but in the latter there is modification of the vascular capacity.

Lesions Simulating Arteriovenous Fistula. This absence of change in pulse pressure is not only pathognomonic of the lesion, but it also serves to differentiate between arteriovenous fistula and conditions that may simulate it. The following case illustrates this point.

A healthy young man was wounded by a shot from an automatic pistol. The ball passed through the lower end of Hunter's canal. Over this area there was a painful swelling about 7 cm. long and 4 cm. wide. The region was very sensitive to pressure and over the swollen area there was a loud murmur during the entire cardiac cycle with accentuation during the systole. Over the same area there was a strongly palpable thrill, which was first perceived three days after the accident. There was no venous distention. When the femoral artery on the affected side was compressed the blood pressure as measured in the arm remained 110/70, but the cardiac rate was reduced from 72 to 56. Was this an arteriovenous aneurysm? It was not. In the first place the prompt appearance of the palpable thrill after the accident proved there could be no arteriovenous fistula. As seen in all our cases, about two weeks are required after the wound before a fistula forms. In the second place, the blood pressure was not changed by compression of the femoral artery. There was, it is true, marked slowing of the pulse, which has been repeatedly stated in medical literature to be a sign of arteriovenous fistula, but the slowing of the heart rate seems to be caused by some afferent nerve impulse that is released when the wounded artery is compressed and cannot be linked with any effect on the hydraulics of bloodflow.

At operation there proved to be no arteriovenous communication in this case. The artery and vein were completely severed and all four ends of the two vessels lay free within a blood sac. The free ends of the vein evidently acted as clapper valves and thus prevented blood from entering either the proximal or distal end. The free distal end of the artery how-

ever, had sufficient resistance in its wall so that the lumen remained partly open and thus admitted sufficient affluent blood so that the pulses in the dorsalis pedis and posterior tibial of the affected side were plainly palpable.

Size of the Heart. The size and contour of the heart are very important and a clear exposition of both may lead to a correct diagnosis when the arteriovenous fistula cannot be eliminated by arterial compression on account of pain or inaccessibility. In our first case the fistula was accessible, but it could not be eliminated on account of extreme tenderness to pressure in Scarpa's triangle. The patient's heart was enlarged, as shown by the palpable impulse and dulness to the left of the midclavicular line. The area and force of the cardiac contact with the anterior thoracic wall were much increased, as shown by the broad quadrilateral impulse that was plainly palpable over the entire anterior area of the right ventricle. In spite of the enlarged heart, high venous pressure and great hepatic pulse we were skeptical on myocardial incompetence as a causative factor, because there were no evidences for stasis in the pulmonary vessels, and the precordial area of dulness did not extend to the right of the sternum, nor was there any evidence for flattening of the subcardial diaphragm to the right of the median line. It seemed there was much enlargement of the ventricles, but no evidence of ectasis of the auricles, and it was purely because there was no evidence for pulmonary stasis or for enlargement of the right auricle that we advised operation. Immediately after the operation the broad area of cardiac impulse over the right ventricle ceased. The contact of the right ventricle with the chest wall was much less vigorous, but the precordial area of dulness was unchanged until two weeks after the operation, when the heart returned to its normal size.

The following case well illustrates the need of interpreting the size and contour of the heart when the arteriovenous fistula is beyond digital control:

The patient was seen by one of us (C. F. H.) a month before the first patient described in this paper came under our observation, and indeed it was not until the second experience that the former case could be satisfactorily interpreted. The patient was a young man, aged twenty-five

years, who two months before was struck with great violence just above the right sternoclavicular joint by the handle of a mop. There was no wound of the skin and no immediate results to indicate there had been a serious injury. Two weeks later the patient suddenly developed a sense of extreme fulness and oppression over the upper thorax, which was caused by the establishment of a communication between the carotid artery and the jugular vein, very close to the innominate vessels. The jugular vein and bulbus venosus were greatly distended and pulsated violently and synchronously with the arterial pulse. The liver was four fingers' breadth below the costal margin in the nipple-line and showed a strong systolic pulsation. The impulse of the left and right ventricle was greatly increased

Fig. 6.—This shows the globular enlargement of the heart of a patient who had an *A–V* communication between the common carotid and the internal jugular.

in intensity and the area of the heart extended to the left midway between the nipple and anterior axillary lines. The area of heart dulness did not extend to the right of the sternum in the third, fourth and fifth interspaces, but there was an area of dulness like a band about 2 cm. wide to the right of the manubrium from the first to the third ribs.

With all this combination of cardiac enlargement, venous engorgement and hepatic pulsation there was no evidence of pulmonary rigidity or edema, and there were also no evidences of flattening of the subcardial diaphragm to the right of the median line. The entire right costal margin moved laterad in inspiration. The inner part of the left costal margin was slightly diminished in its laterad movement, but the outer half moved

readily outward in inspiration. During systole and diastole there was a loud murmur audible, which had its maximum intensity at the right border of the manubrium. The pulse had a celer character of moderate excursion. Fig. 6 is a skiagram taken at the time and shows the moderate globular enlargement of the heart.

A few weeks later surgical relief was attempted, but the patient succumbed during the operation.

Although this patient exhibited such marked signs of venous and hepatic stasis, he was able to walk about, and although he could exercise very little, he did not suffer from air hunger when at rest. These facts, together with the want of pulmonary edema and the absence of ectasis of the right auricle, justified the diagnosis of arteriovenous fistula. The location and contour of the right heart border and the inferior contour of the heart, as revealed by the movements of the costal borders, are the essentials in making a diagnosis in such cases as this. For one may be greatly misled if the presence of cardiac enlargement, pulsus celer and the murmurs is accepted as proof of venous stasis from cardiac incompetence.

Cardiac Enlargement. The behavior of the heart in arteriovenous fistula is amazing. The large and vigorous impulse that takes in the entire precordial aspect of both ventricles may lead one to overestimate the size of the heart and erroneously make a diagnosis of cardiectasis. When the A–V opening is closed the impulse over the area of the right ventricle ceases immediately and only the apical impulse of the left ventricle is perceptible. This change occurs directly upon the closing of the arteriovenous fistula, but in severe cases, like the first one described, the percussion borders will not return to the normal limits until after two weeks. In our second case, which was complicated with arteriosclerosis, this change in the character of the precordial impulse could be produced at will by alternately compressing and releasing the femoral artery above the site of the fistula. When the A–V communication is open the diastolic-systolic excursion of the heart is increased and the heart assumes a globular contour, although the area of precordial projection may be little changed. The deception is quite like that experienced in estimating the size of the heart in acute Graves' disease. The examiner is very likely to overestimate the size of the heart in

this disease, because the systolic excursion is increased to accommodate an increased minute volume-flow of blood. The impulse becomes accessible over the entire precordial area and the heart is therefore assumed to be much enlarged. Only accurate percussion of the borders of the heart and study of the costal margin movements save one from this error. In acute Graves' disease study of the costal margin movements never indicate any flattening of the subcardial diaphragm. In chronic Graves' disease that presents evidences of myocardial decompensation and renal disease the subcardial diaphragm will be flattened just as occurs in cardiectasis from other causes.

In producing these cardiac changes experimentally we had no success in survival experiments for the same reason that in such experiments we could not get any very great changes in blood pressure, viz., the A–V leak was insufficient. However, when the proximal ends of the abdominal aorta and cava were united by a U-tube and the thorax and pericardium opened we had a satisfactory view of the two ventricles and the right auricle, and the changes in the size and excursion of these parts were plainly in view as the A-V communication was alternately closed and opened by compressing and releasing the abdominal aorta. Under the fluoroscope the heart was seen to swell into a globular contour, but was little enlarged. Skiagrams were then taken with the tube six feet away. Fig. 7, A and B, shows the difference in contour of the heart when the A–V flow was closed and free. Later the thorax was freely opened, artificial respiration begun and the pericardial sac opened and used as a support on which the heart rested. With opening and closing the A–V path the heart was seen to respond in a manner that suggested the changes in excursion and celerity of the arterial wall from the same cause. The ventricles visibly swelled and greatly increased their excursion as the communication was opened, but the right auricle increased very little in size and showed a comparatively slight increase of diastolic-systolic excursion. The increase in volume and excursion of the ventricles was plainly a compensatory effect to meet the need of the increased cardiac output that resulted from the arterial leak. Ten cc of 1 to 1000 adrenalin were then injected into the jugular vein at intervals of ten minutes.

The first few injections caused the heart to increase in size and the aorta became greatly distended and elongated, so that it resembled the elongated and dilated sclerosed aorta in patients with a high degree of peripheral arterial resistance. After several repetitions of the adrenalin injections, the heart dilated from incompetence and went into fibrillation of auricle and ventricle. As decompensation occurred, attended by great ectasis of the right ventricle and auricle, one perceived the striking contrast between ectasis of the

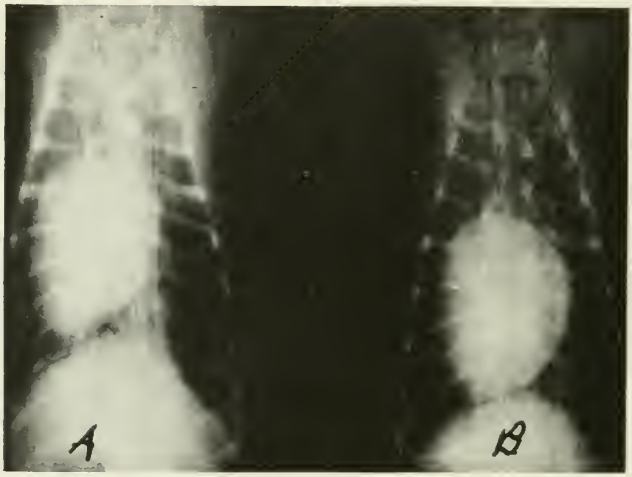

FIG. 7.—A teleroentgenogram of the heart of a dog in which there was an A–V communication between the abdodinal aorta and the cava. The communication was made by means of a U-tube connecting the proximal ends of the aorta and cava. *A* is the heart when the communication was closed and *B* when the communication was opened.

heart chambers and compensatory dilatation in response to an increase of minute volume-flow. Why the subcardial diaphragm is flattened in ectasis and not in compensatory dilatation was apparent. In cardiectasis there is great enlargement and downward extension of the right auricle and base of the right ventricle, whereas in compensatory dilatation there was an increase in the circumference of the mesocardium but no depression of the ventricular base or of the auricle as the circumference of the ventricle enlarged.

Cardiac enlargement compensatory for an increased volume-

flow produces a globular enlargement restricted to the mesocardium. There is slight if any dislocation of the apex and the circumference at the base of the heart and at the atrioventricular sulcus is not increased. The heart remains in an erect position and does not encroach on the diaphragm. In arteriovenous fistula, chlorosis and acute Graves' disease the heart takes on this globular contour and increase of its middle circumference in response to the enlarged minute volume-flow of blood. The diastolic-systolic excursion of the ventricles is enlarged. The force and area of precordial excursion of the ventricles are greatly increased and give the impression of great cardiac dilatation, when in reality percussion, movement of costal borders, and the *x*-ray all indicate only a moderate globular enlargement of the ventricles. In acute Graves' disease a degree of volume increase that would suffice in myocardial disease to depress the subcardial diaphragm will not show any modification of inspiratory movements of either costal border. The reason for this is quite apparent if the changes are observed in heart volume and contour when adrenalin in large amounts is given to a dog with a large A–V fistula. When the fistula is open the heart increases in its midcircumference and diastolic-systolic excursion without encroaching downward, but as acute dilatation and fibrillation follow the the large dosage of adrenalin, the circumference of the ventricles at the atrioventricular sulcus greatly enlarges, the right auricle protrudes with a large semilunar contour to the right of the base of the ventricle and the heart encroaches on the diaphragm. These observations provided us with a satisfactory explanation for the discrepancy between the costal border movements in Graves' disease and in cardiac disease, when apparently both conditions should produce corresponding effects on the costal border movements.

From our clinical observations and animal experiment we were convinced of the ventricular enlargement that immediately attends short-circuiting of the circulation through an A–V opening. When the teleroentgenograms were made, however, they were disappointing. They did not show as much enlargement in the transverse direction as we expected to see. The cardiac enlargement as perceived by clinical examination and by direct inspection in animal experiments indicated the primary enlargement to be chiefly in an

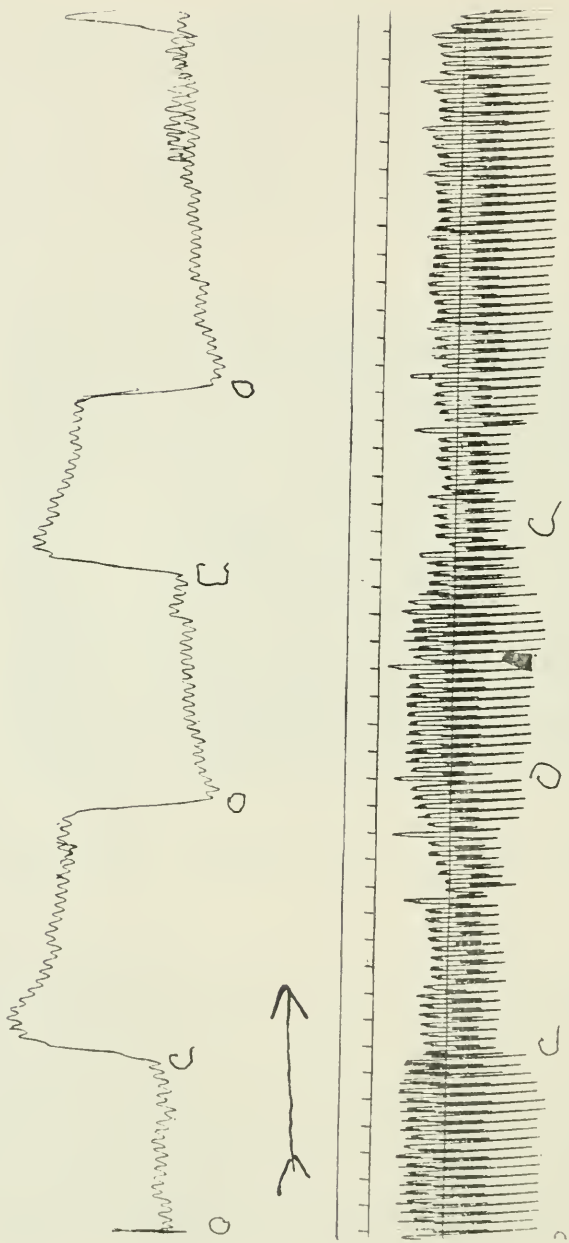

FIG. 8.—The lower tracing is from a cardiac plethysmograph. The upper line traces the arterial pressure. *c* marks the point where the communication between the aorta and cava was closed and *o* the point where the communication was opened.

anteroposterior diameter in the early stages of the disease and this enlargement of the transverse diameter to be a later development.

To present graphic evidence of ventricular enlargement as a promptly developing sign of A–V fistula the size of the heart was recorded by a plethysmograph. The abdominal aorta and cava were united by a U-tube, the thorax opened and artificial respiration employed. The ventricles only were included in the plethysmograph. The upper tracing in Fig. 8 shows the blood pressure taken by a mercury manometer from the carotid artery. The lower tracing is that of the plethysmograph. *C* marks the closure and *O* the opening of the A–V communication. The excursions of the plethysmograph were graduated immediately after the experiment by introducing measured quantities of water into the system. When the results of the graduation were applied to the tracings it was found that the excursion of this heart amounted to 6 cc when the A–V opening was closed and 11 cc when opened. This measurement is in all probability exaggerated by the swing of the registering lever, but it is not at all surprising after the change in excursion has been observed in an animal experiment. The time marker is in seconds.

Fig. 9 is a tracing taken on a fast drum to show the working of the plethysmograph. The up-stroke traces diastole and the down-stroke systole.

These observations show how a heart may be enlarged anteroposteriorly and fail to show by percussion or *x*-ray any transverse enlargement. This is true of well-compensated cases of mitral stenosis when only the right ventricle is enlarged, and it is also true in Graves' disease, where both ventricles are enlarged and the auricles are not. The only physical sign that betrays the enlargement is the enlargement of the area of precordial impulse due to the right ventricle partaking of this activity as well as the apex of the left ventricle. When a clinician establishes the evidences for anteroposterior cardiac enlargement he should not recede from his position because the *x*-ray fails to reveal an enlargement of the precordial area.

Hepatic Pulse. The physical sign of striking importance that remains for discussion is the hepatic pulse. It will be remembered

FIG. 9.—The upper line is from the plethysmograph of a dog's heart under the operative conditions described below Fig. 8. This tracing is on a fast drum and simply shows the character of the plethysmographic tracing. The up-stroke traces diastole and the down-stroke systole.

that in 3 of the reported cases—the 2 in which the A–V fistulæ formed in the femoral vessels after gunshot wounds and the 1 in which the fistula formed between the carotid and jugular after a sharp blow from the long wooden handle of a mop—there were systolic pulsations in the liver. In the case of the woman with a gunshot wound, as the artery above the fistula was compressed the hepatic pulse disappeared with the cardiac systole that followed the arterial compression, so that there can be no doubt that the systole of the right ventricle played no part in producing the hepatic pulse. It depended on two factors, viz., an adequate distention of the cava and a direct pulse wave from the artery into the tributaries of the cava. In our experimental animals there was no hepatic pulse palpable or visible when the abdomen was opened and the liver brought plainly into view, and in none of them were we able to procure sufficient pressure in the cava to obtain a hepatic pulse. It might have been expected that when the lumen of the aorta was connected with the cava there would be a considerable rise in the cava pressure, but that was not the case. Our experiment was of such short duration that the increased output of the heart was adequate to care for this contingency. In the clinical cases the problem of hydraulics of blood-flow must have been nearly, although not quite, identical with that in our experimental animal, the essential factor being the cardiac inability to compensate over a prolonged period for the enlarged minute volume-flow necessitated by the arteriovenous communication.

The hepatic pulsation in our patients was not an index or measure of cardiac decompensation. It came directly from the arteriovenous opening, but should the arteriovenous leak be ever so large, that alone will not suffice to produce a hepatic pulse. The pulsation of the liver is not obtained until there is added the factor of large elevation in venous pressure. The arteriovenous leak does not suffice to produce the liver pulse until the cava pressure increases as a result of the incompetence of the heart to supply the increased output demanded as a result from the arteriovenous fistula. Under such conditions, closure of an arteriovenous communication produces an amazing cure. By this procedure the venous system as well as the myocardium profits directly. The work of the heart is

greatly lessened and both the direct and the indirect source for venous stasis is corrected. Our patient, who was operated and promptly restored to health after so long and exhausting an illness, submitted to an examination two years after the operation. He was then in perfect health and seemingly was concerned only about his pension, which had been granted on the basis of total disability.

THE PREVENTION OF CERTAIN FORMS OF CHRONIC CARDIAC VALVULAR DISEASE[1]

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Until recently perhaps few persons, even physicians of long experience in large general hospitals, have realized the magnitude of the "cardiac problem" from whatever standpoint it be approached. Heart disease has become, in this country at least, the most important of the causes of death. According to the estimate of Knight,[2] some 180,000 persons in continental United States and Canada died last year of heart disease.

Tables and estimates of mortality, however, give but incomplete evidence of the prevalence of heart disease, because many deaths returned as from pneumonia and other infections, for example, probably would not have occurred except for coexisting disease of the heart.

It has been estimated that 200,000 children of school age in the United States have heart disease.

Facts such as these make it apparent that heart disease is perhaps the most pressing public health problem confronting the medical profession today, and because of the magnitude of the problem any contribution to its solution is to be welcomed.

The conception that endocarditis might heal without crippling the heart first presented itself to me in 1897,[3] when I had under my

[1] From the Department of Medicine, University and Bellevue Hospital Medical College.

[2] Life Waste in 1922: Its Warning and its Lesson. Proceedings of the 16th Annual Meeting of the Association of Life Insurance Presidents, New York, 1922, p. 25.

[3] Acute Infective Endocarditis Following Vaccination: Recovery, Philadelphia Medical Journal, 1900, vi, 1193.

care a patient with endocarditis who recovered and whose heart was found to be normal two and a half years afterward. An obvious corollary from this conception is that if any means can be found of hastening the healing of the valves, it might be possible to prevent the development of chronic valvular disease in at least some cases. Since 1897 these questions have engaged my attention.

Before proceeding further, it will be advisable to define the limits of the discussion and the significance of some of the terms which will be employed.

The following discussion is based entirely on clinical observations and, while aware of the frequency with which the myocardium becomes involved along with the valves in endocarditis, it is to the valves especially that I would direct attention.

The forms of heart disease here referred to are those occurring for the most part in children, adolescents and young adults, which are infective in nature, and which, for lack of more precise knowledge, may be classified broadly as "rheumatic." The term "endocarditis" will be restricted to an existing inflammation of the endocardium. The term "chronic valvular disease" will denote permanent deformity of a valve or valves which interferes with their proper functioning.

All previous attempts to prevent these forms of heart disease have been limited, so far as a careful search of the literature reveals, to the removal of foci from which infections of the endocardium are believed to arise and to the closing of supposed atria of infection. Such attempts at prevention are of great importance, but years of trial will be required to test their effectiveness.

The plan to which I wish to direct attention relates rather to the management of cases after infection of the valve has occurred and is based upon the assumption that inflamed cardiac valves are capable of successful repair.

Healing of the Inflamed Endocardium. Clinical observation long ago led to the belief that the inflamed endocardium is capable of healing; the demonstration postmortem of the process of repair in operation or completed removes all doubt concerning the question.

The frequency with which the endocardium heals, however,

seems scarcely to be realized. My own belief is that healing occurs in the great majority of cases of rheumatic endocarditis; exceptions to be mentioned are the cases cut short by accidents such as embolism and by unusual myocardial involvement. There is also the possibility that in some cases a low-grade inflammatory process becomes established and persists perhaps for years. Unless the inflamed valves in the rheumatic forms of endocarditis heal it would be difficult to explain the large number of cases of chronic valvular disease in adults, the beginnings of which may be traced to childhood. In fact, the very deformities of the valves may be adduced as evidence that the valves have healed even though the result is failure from the physiological standpoint.

Healing of the Valves without Deformity. In endocarditis the normal functioning of the valves may be impaired in at least two ways: (1) By vegetations so situated that they prevent perfect adaptation of the cusps or leaflets and by (2) swelling and distortion of the segments. In either case a murmur would probably develop; in both cases it is conceivable that the murmurs might disappear when the valves heal—that is after the shrinking of vegetations, the subsidence of the swelling and the return of flexibility to the leaflets the competency of the valve may be completely restored. On no other hypothesis can the disappearance of obstructive murmurs (mitral presystolic and aortic systolic) which develop during an attack of rheumatic fever, weeks or perhaps months after the attack has subsided, be explained.

When valves heal without sufficient deformity to produce a murmur there may remain no clinical evidence of previous disease unless such evidence results from coincident involvement of the myocardium. To illustrate this fact, the following typical case may be cited:

A boy, aged thirteen years, in 1909 developed acute endocarditis with slight fever (99° to 100° F.) and moderate anemia. At various times during his illness three cardiac murmurs appeared (mitral presystolic, mitral systolic and aortic systolic) which were not constantly present.

Although the disease persisted for nearly two years the boy made a complete recovery and has remained well. He entered the army as a private in July, 1918, was put through the usual routine, suffered from a severe

attack of influenza during his service and was discharged as "fit" in January, 1919. In February, I found the left border of his heart 1.5 cm. within the nipple-line, with normal rhythm and no murmurs. On April 26, 1923, the left border of the heart was still well within the nipple-line; there were no murmurs and the exercise reaction was normal. In this patient's history is to be found the only clue to the previous attack of endocarditis.

There is a type of case, however, following endocarditis which is directly referable to the temporary incompetency of the valves, although possibly in part to coincident myocarditis. I refer to cases of cardiac enlargement (hypertrophy or dilation, or both) in early life, without murmurs, for which none of the commonly accepted causes of enlargement may be found. The following case may be cited as a typical example:

A boy, aged five years, during an attack of chorea developed aortic systolic, mitral presystolic and mitral systolic murmurs, with hypertrophy and dilatation. The left border of the heart extended well beyond the nipple-line. A year later all the murmurs had disappeared, though the hypertrophy (and dilatation) persisted.

At the last examination (two years later) the enlargement was the only remaining evidence of previous disease of the heart.

In cases such as this the hypertrophy remains after the valves have healed and the murmurs have disappeared. How long such hypertrophy may persist must be left, for the present, an open question, though I am disposed to think it may be permanent. The following case lends support to this opinion:

A boy, aged ten years, with infected tonsils and enlarged adenoids, developed endocarditis with murmurs. Exercise was restricted until he was twenty-one years old. In 1923, in his twenty-eighth year, no murmurs are present but the heart is markedly hypertrophied, measuring 3.5 cm. to the right and 11.5 cm. to the left of the midline (3.5 cm. outside of the nipple-line).

I believe that cases of hypertrophy originating during the course of endocarditis which heals without deformity of the valves are relatively common. At least since my attention has been directed

to this form of hypertrophy I have seen an increasing number of cases which could be most easily explained on such an hypothesis.

This type of case also has a direct bearing on the question of the so-called "athlete's" heart, but it would lead too far to discuss the matter at this time.

Permanent Deformity. When permanent deformity of a cardiac valve is not due to destruction of a portion of the valve it is attributable directly to the process of repair. Vegetations are organized (and possibly calcified), adjacent segments (or chordæ) fuse and leaflets are thickened and distorted by scar tissue.

It is probable that in the process of repair in the endocardium, the amount of new connective tissue formed is proportional to the extent of the original injury and to the duration of the inflammatory process. After the lighter grades of endocarditis the function of the valve may be completely restored, as has been pointed out; when the injury is more severe or the inflammation more prolonged the valve may be distorted to such a degree that it is rendered permanently incompetent, and the slow contraction of the scar tissue serves only to increase the deformity.

There is still another way in this group of cases in which the cardiac valves may become permanently deformed, that is, through recurrent attacks of endocarditis. As is well known from clinical and pathological observations, damaged valves readily become reinfected and each succeeding attack of endocarditis leaves behind its increment of scar tissue to cause or to increase an existing deformity. Statistics are not yet available to indicate what proportion of cases of healed endocarditis become reinfected, but it is probably large.

For the purpose of bringing out information concerning the etiological relationship of recurrent attacks of endocarditis to chronic valvular disease, several years ago I requested Dr. Douglas Symmers to bear the question in mind in autopsies upon patients dying of or with these diseases. He has given me the following statement:

"It is a matter of not infrequent observation at autopsy that the heart valves, particularly those on the left side, exhibit sclerotic or even calcific changes without anatomical indications or a clinical history of functional disturbances. This, I think, is due to the fact that all of the heart valves are larger than is actually necessary in order to meet the demands made

upon them; that is to say, that, above the line of closure, there is a quantity of valve tissue which must be dispensed with before regurgitation can occur; and, on the other hand, that sclerotic heart valves commonly offer no stenosis to the normal passage of blood. Sclerosis of the heart valve in these circumstances represents the end-stage of the process of healing. That sclerotic heart valves may be reinfected is shown by the not infrequent discovery at autopsy of vegetations on them in different stages of repair. By this I mean to say that there is anatomical evidence which indicates that an individual may recover from an attack of valvulitis, sustaining sclerosis of the valve but without impairment of its function; secondly, that a sclerotic valve may become reinfected on one or more occasions, and that, ultimately, function is impaired as a result of retraction on the one hand or stenosis on the other."

From my clinical experience I am inclined to believe that recurrent attacks of endocarditis play a not inconspicuous role in the development of chronic valvular disease. The sequence of events was clearly illustrated in the following case:

A boy, eleven years old, whose tonsils had been removed in his fifth year and his adenoids in his eighth year, developed an attack of rheumatic fever in April, 1919.

The mitral and aortic valves were affected during this attack and aortic obstructive and double mitral murmurs appeared.

By June, 1920, the murmurs had disappeared; the heart was of normal size and the exercise-reaction was normal. Again, in December, 1920, the heart was found to be normal in every respect.

In January, 1921, at boarding school, the boy was put to bed for a "cold." While in bed he developed severe pains in the muscles of the thighs, which lasted for four days. After being up and about for a few days, his heart suddenly dilated and his condition caused great alarm. At the Easter vacation (when I saw him) there were a systolic and a diastolic murmur at the aortic orifice, with mitral regurgitation and marked enlargement of the heart.

December, 1922. Both aortic murmurs are present and the enlargement of the heart persists.

Clearly then in this case the first attack of endocarditis healed with complete restoration of the function of the aortic and mitral valves. Though the valves undoubtedly bore scars from the recent inflammation, their repair had been successful from the physiological point of view. The second attack of endocarditis, however, has

caused what so far appears to be permanent deformity. Whether the aortic valve may again become competent only the future will determine—just a little more than a year has elapsed since the second attack of endocarditis.

Diagnosis. Based, as my suggestions are, upon the conviction that inflamed cardiac valves possess the power of healing, that their healing may be promoted and that the tendency to recurrent attacks of inflammation may be lessened, it is obvious that success in the treatment of endocarditis stands in close relationship to the early recognition of the condition.

In the absence of murmurs the existence of endocarditis may only be suspected; but, as is well known, not all cardiac murmurs have a pathological basis—the organic must be differentiated from functional murmurs. I shall not attempt at this time to evaluate the various criteria which have been put forward as characteristic respectively of functional and organic murmurs. I shall say only that I feel far less confident than formerly of being able to distinguish them.

The early diagnosis of endocarditis does not rest upon examination of the heart alone. Evidences of a constitutional reaction must be sought, and they may appear insignificant. Approaching the diagnosis from this direction, if a child or adolescent is reported to be out-of-sorts, or is anemic, or exhibits a low-grade, continuous or recurring fever (say 99° to 100° F.), for which no obvious cause can be found, careful attention should be given to the possible existence of endocarditis. Such patients should not be dismissed with the diagnosis of an "ailment of childhood" and the comforting advice to the parents that "he will outgrow it." The history of the patient may furnish important clues to a correct diagnosis, and such information as may be obtained from the blood picture or blood cultures should be utilized.

The diagnosis of recurrent attacks of endocarditis rests upon essentially similar considerations.

No less important than the early recognition of endocarditis is the determination of the approximate time at which the inflammation subsides. The difficulties which stand in the way are obvious. The persistence of murmurs cannot be interpreted to mean that

inflammation is still present. On the contrary, however, the persistence of constitutional symptoms undoubtedly signifies that the inflammatory process is still active. The prolongation of apparent convalescence will always bear most careful investigation. Yet after all has been said the question, "Have the valves healed?" must not infrequently remain unanswered; and treatment should not permanently be interrupted until this question may be answered with reasonable assurance in the affirmative.

Treatment. There are two main objectives in the treatment of endocarditis: (1) The reduction of the work of the heart to a minimum and (2) the protection of the patient from all influences which may lower resistance, especially exposure.

These objectives may be reached only by keeping the patient in bed. Rest in bed usually reduces the rate of the heart, often as many as twenty or more beats per minute, and lessens the injury to the valves, which is incident to their closure. The dire consequences of exposure to patients recently recovered from acute articular rheumatism furnish a strong argument in favor of maintaining the body of a patient with rheumatic endocarditis at an equable temperature. Other analogies may readily be called to mind.

The mere recommendation of rest in bed for patients with endocarditis, of course, presents nothing new. In cases of endocarditis with active fever, or with serious involvement of the myocardium, or which develop in the course of rheumatic fever, the necessity of putting the patient to bed is obvious. But it is not primarily such cases which I have in mind; it is rather those with murmurs which, upon superficial examination, might be interpreted as functional and in which the constitutional reaction will escape attention unless seemingly insignificant symptoms are given their true perspective. If the patient is not put to bed and kept there, the cardiac valves are not given the fullest opportunity to heal, the inflammatory process is prolonged and recurrent attacks of endocarditis are invited. The progressive course of many cases of mitral stenosis, for example, seems scarcely due to the injury wrought by a single attack of endocarditis of even relatively long duration.

The length of time which patients with rheumatic endocarditis should be kept in bed varies with each case. The only general

recommendation which is applicable to all is that no patient should be allowed to get up until after the disappearance of the constitutional symptoms. At times a slight relative increase in the polymorphonuclear cells may be the only evidence that the constitutional reaction has not subsided.

In my own experience the duration of the confinement to bed has varied from several months to two years. When the longer periods of rest are necessary, one of the most difficult problems is to gain the coöperation of the parents. The decision to permit a patient to get up must always be tentative. At first the same close supervision as when the patient was in bed is necessary and at the return of any unfavorable symptoms the bed-treatment must be resumed. Healing valves readily become reinfected and ample time should be allowed for their recovery.

In the case of the first patient mentioned above the constitutional symptoms persisted for nearly eighteen months. He was then allowed to get up. The symptoms quickly returned, however, and he was put back to bed, where he remained for six months more. When at last he was gotten out of bed he was unable to stand, but with massage and carefully regulated exercises the power of the muscles soon returned. For the next six years the boy's activities were carefully supervised, that is until 1917. Since there have been no restriction whatever upon him.

If justification for such a plan of treatment be required, the answer is that the spending of two years of one's childhood or youth in bed is not an excessive price to pay for a normal heart.

All patients who have had acute or recurrent attacks of endocarditis, especially children and adolescents, should be kept under observation for years. Nor should they be dismissed even after thorough examination of the heart until the next periodical examination of the heart. Examinations of the blood and careful readings of the body temperature extending over several weeks should be made at intervals and be submitted to the physician. Only in this way may the earliest stages of recurrent attacks be detected, and recurrences should be treated in the same manner as first attacks.

Conclusions. 1. In rheumatic endocarditis the tendency of the inflamed valves is to heal; they may heal without deformity and there may remain no clinical evidence of previous disease, or the heart may remain enlarged as a result of the temporary incompetency of the valves.

2. The permanent deformity of the cardiac valves in probably many cases of chronic valvular disease is due to recurrent attacks of endocarditis.

3. Healing of the valves is promoted by keeping the patient in bed; this treatment should be maintained until after the disappearance of all constitutional symptoms.

DISCUSSION

Dr. Harlow Brooks, New York: We can verify these remarks as to repair of the valves in endocarditis or by biopsy experience. Some of our cured cases have a history of endocarditis, but some have no such history. We will also emphasize particularly the importance of rest in known endocarditis, in the hope that favorable result may follow. Rest acts in two ways: It gives the valve a chance to repair, and it also conserves the diseased muscle which is usually more or less involved.

Dr. Henry Koplik, New York: The murmur may appear and reappear in these cases. We should be cautious in pronouncing a child free from cardiac disease until repeated examinations have been made over long periods of time. I have been frequently impressed with this fact. The first president of this Association, Dr. Delafield, emphasized this point. Prolonged confinement by rest in bed, especially in children, should be avoided. In many such cases confinement in bed may run the patient into another condition, which is as bad, that is the accumulation of large masses of adipose. The murmur may disappear, but will reappear when the patient is allowed to get up. If the period of confinement to bed is limited, it will avoid degeneration of tissues.

Dr. W. S. Thayer, Baltimore: The problem in children is not exactly the same as in adults. In adults, rest in bed is vital during an acute endocarditis. The danger of too great a gain in weight should be avoided by suitable dietetic and physical methods. In children it is often difficult to keep the patient so completely at rest and ill-considered attempts

so to do may indeed involve unnecessary strain on the circulatory apparatus. But when children or young people are kept for long periods in bed the same care should be taken as to diet and physical treatment as in adults. Some years ago a young girl, about at puberty, was brought to my consulting room. During a mild rheumatic endocarditis she had been kept in bed for a period of several months and so overnourished that she had become extremely fat—so fat that atrophic striæ had appeared all over her body. Now, a charming girl in her twenties, the skin of her neck, chest and arms is cruelly disfigured.

A HITHERTO UNDESCRIBED FORM OF VALVULAR AND MURAL ENDOCARDITIS*

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In previous communications[1] cases of endocarditis were classified as rheumatic, syphilitic, acute bacterial and subacute bacterial. We have introduced the designation "indeterminate" for an additional group of cases concerning which very little is known. The term is used to include (*a*) the cases of so-called "terminal" endocarditis and (*b*) cases of atypical verrucous endocarditis. The object of the present communication is to discuss the cases included in the latter group, which we believe represent a hitherto undescribed form of endocarditis.

In a study of the postmortem material of the Mount Sinai Hospital, two cases of endocarditis were encountered which showed valvular and mural lesions of a peculiar type. These lesions were free from bacteria when studied by the usual methods and differed in morphology and localization from those found in rheumatic and subacute bacterial endocarditis as well as other forms of endocarditis. Moreover, both cases showed fibrinous pericarditis, but there were no Ashoff bodies in the myocardium. Because of the unusual character of the endocardial lesions and their verrucous appearance, these cases were designated: "atypical verrucous" endocarditis. When this form of endocarditis is better understood a more appropriate nomenclature will doubtless be introduced.

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More recently we had the opportunity of studying two additional fatal cases, the clinical histories and postmortem examinations of which are recorded below. For purposes of brevity, the findings in the first two cases only will be presented in summarized form. At a later time, we shall publish the complete records of all our cases.

Case I.—S. H., (Admission No. 216669), female, aged twenty-four years, married, was admitted to the Mount Sinai Hospital on January 21, 1922. The family history was negative. The only previous illness which she remembered was an attack of polyarthritis three years before. Her present illness began six weeks before admission with sticking precordial pain. Two weeks later her knees, ankles, wrists, elbows and shoulder-joints became swollen and painful. At the same time she developed a chill and fever. Her face became so swollen that her eyes were practically closed. Her urine was scanty, her blood-pressure was elevated and she experienced "drawing" pains in the left lumbar region. A week before admission she began to complain of sore throat. The edema of the face diminished, but the precordial and articular pain persisted.

Examination. The patient was poorly nourished, acutely ill and febrile (temperature, 103.6°). There was slight puffiness of the face. Petechiæ, some of which had white centers, were found in the conjunctival mucous membrane of both lower lids and on the anterior aspect of the thorax and both sides of the neck. The tonsils were moderately enlarged and congested. The lungs were negative. The heart was not enlarged and the action was accelerated but regular. The first sound at the apex was increased in intensity. A systolic murmur was audible over the entire precordium and left axilla. The second pulmonic sound was accentuated. The blood-pressure was 145 systolic and 90 diastolic. The abdomen was distended and held rigidly and there was pain and tenderness in the left hypochondrium, symptoms pointing to splenic infarction. The spleen was not palpable. The left elbow and both ankle-joints were swollen and tender. The metacarpophalangeal joints of the left hand were tender and painful, but although there was no swelling, the overlying skin had a peculiar red color. There was erythema and induration of the skin and cutaneous and muscular tenderness over the extensor surface of both forearms.

The blood count showed: Red blood cells, 5,400,000 per cu. mm.; hemoglobin, 84 per cent. White blood cells, 6500 per cu. mm.; polymorphonuclear neutrophilic leukocytes, 84 per cent; eosinophiles, 1 per cent; lymphocytes, 13 per cent; monocytes, 2 per cent. The Wassermann reaction was negative. The phenolsulphonephthalein output was 50 per cent in two hours.

Course. In the following week the joint pains improved and the dermatomyositis disappeared. The temperature continued to be elevated, reaching 101° to 103° daily. Albumin and hyaline and granular casts were present in the urine, and there was persistent oliguria. At first there were no erythrocytes in the urinary sediment and the blood showed normal nitrogen figures; later, microscopic hematuria appeared and the blood showed moderate nitrogen retention. Crops of white-centered petechiæ recurred at frequent intervals. The articular pains returned from time to time. On February 8 a pericardial friction rub became audible and there was a return of the intense precordial pain from which the patient had suffered prior to her admission to the hospital. On February 17 the temperature rose to 104°. In the meantime signs of fluid in the chest had appeared, and on February 19, 250 cu. cm. of clear, yellowish fluid were withdrawn from the right pleural cavity and 20 cu. cm. of blood-tinged fluid from the left. The fluid from both sides was sterile. On the following day the temperature fell to 99.8°, and from this time on, with only occasional exceptions, the temperature remained below 101°. Ascites now appeared and the fluid in the chest reaccumulated.

The patient had become progressively more anemic, and on March 6, the erythrocyte count had fallen to 2,088,000 per cu. mm. and the hemoglobin percentage to 34. The leukocytes now numbered 13,400 per cu. mm., 79 per cent of which were polymorphonuclear neutrophils. On March 10 a bed-sore appeared over the sacrum and later others developed. From time to time the patient complained of severe pain in the epigastrium and left hypochondrium and over the precordium. Vomiting set in and occasionally the vomitus contained blood. On March 20 the patient became dyspneic, the albuminuria increased and the breath became uremic. The ascitic effusion had increased to such an extent that it was necessary to tap the patient. Accordingly, on March 22, 1500 cu. cm. of clear, straw-colored fluid were removed from the peritoneal cavity. On April 3 the phenolsulphonephthalein output was 5 per cent in two hours. The following day the patient had a convulsion, following which she complained of severe precordial pain. Two days later she had a second convulsion, following which she developed an attack of pulmonary edema. One week later a second abdominal paracentesis was performed and 5000 cu. cm. of fluid were withdrawn. On May 3 a diffuse herpetic eruption appeared below the left breast and scapula. The subcutaneous edema had now become generalized and the pericardial friction rub could again be heard. The temperature no longer rose above 99° and was often subnormal. In the last three weeks of the patient's life she frequently complained of severe epigastric and precordial pain. The daily urinary output fell below 500 cu. cm. On May 31 she suddenly developed dyspnea and cyanosis. The pulse became very rapid and irregular and she became stuporous and died.

Four blood cultures were made, all with negative results. The methods employed were those which generally gave positive results in cases of subacute bacterial endocarditis.

It was evident that the patient was suffering from a subacute febrile illness which began with renal manifestations and that some form of endocarditis was present. The main features were the onset with acute nephritis, the protracted course with long-continued fever and progressive anemia, acute pericarditis, mitral insufficiency, recurrent crops of white-centered petechiæ, articular symptoms, nitrogen retention, abdominal pain and hematemeses, symptoms of splenic infarction, dermatomyositis, herpes zoster and negative blood cultures.

The clinical picture was unique and it was difficult to arrive at a diagnosis which satisfactorily explained all the symptoms. The differential diagnosis was apparently between rheumatic and subacute bacterial endocarditis. The pericarditis, arthritis and negative blood cultures spoke for the former diagnosis, whereas the white-centered petechiæ, splenic infarction and glomerulonephritis pointed to the latter. Accordingly, the most probable diagnosis appeared to be a combined infection caused by the etiologic agents of both diseases. Assuming the diagnosis to be correct, it was difficult to explain the occurrence of acute nephritis at the onset of the disease, inasmuch as acute nephritis occurring in subacute bacterial endocarditis develops only when the latter disease is well established. The postmortem examination showed that neither rheumatic nor subacute bacterial endocarditis was present, but revealed instead the lesions which we believe are characteristic of the atypical form of verrucous endocarditis.

Summary of Autopsy Findings. Heart: Weight, 360 grams. There was an organizing fibrinous pericarditis, with partial obliteration of the pericardial sac. The tricuspid valve showed a discontinuous, fibrous thickening, representing a healed organic lesion. There were several minute vegetations along the line of closure. The mitral valve showed a fairly continuous thickening involving the closure line and free edge, pointing to a previous attack of endocarditis. Along the line of closure, extending in places to the free edge, there was a row of slightly polypoid, verrucous vegetations, varying in diameter from 0.5 to 2 mm. Their

consistence was fairly firm, and their appearance for the most part slightly translucent and the color grayish. A part of some of the vegetations was opaque and yellowish-gray in color. In addition, the endocardium over the upper part of both papillary muscles of the left ventricle and the intervening mural endocardium was the seat of an inflammatory process. There had also been extension of the endocarditic process from the ventricular aspect of the posterior cusp of the mitral valve near the line of attachment downward for a short distance along the endocardium of the posterior wall of the ventricle. The surface in these areas was apparently denuded of its endothelium and covered by extensive flat patches of thrombus deposit, the deeper layers of which were firmly attached to the underlying myocardium. Near the apex of the ventricle there was a similar patch of mural endocarditis, measuring 2.5 x 3.0 cm. The mural vegetations for the most part had a grayish or reddish-brown color, with here and there a yellowish area. The lesions were irregular in outline and flat and had an opaque, roughened, irregularly fissured surface. On cut section the deeper layers had a grayish, translucent appearance, indicating fibrosis, with irregular extension into the subjacent myocardium. The aortic valve showed a few small, firm, healing vegetations. The heart muscle was pale and brownish in color and showed fine grayish streaking. The coronary arteries showed an inappreciable degree of sclerosis.

The remainder of the findings will be given briefly. There was bilateral, organizing, fibrinous pleurisy with effusion into the left pleural sac, edema and congestion of the lungs, ascites, edema of the lower extremities and decubitus ulcers over the sacrum. The kidneys showed subacute diffuse glomerulonephritis, and in the left kidney there were also a few small abscesses, from which the Staphylococcus aureus was grown. The spleen was small and showed a small healed infarct.

Microscopic examination of the mitral valve showed lesions which were larger than those encountered in rheumatic endocarditis. The greater part of the vegetations consisted of a mass of hyaline thrombus on which was deposited a fresher blood platelet thrombus, the surface of which was only partially covered by endothelium. The patches of mural endocarditis showed extensive deposition of hyalinized blood platelet thrombus, the greater part of which was not covered by endothelium. The endocarditic process had invaded the underlying myocardium rather deeply, with resulting destruction and replacement of many of the muscle fibers. The deeper layers of both the valvular and the mural lesions were diffusely infiltrated with round cells and showed extensive fibrosis, indicating advanced healing. No bacteria were found in any of the vegetations. The heart muscle showed neither Aschoff bodies nor Bracht-Waechter lesions.

A glance at the heart suffices to convince one that the lesions do not correspond to any of the recognized forms of endocarditis. The individual points of difference from the forms of endocarditis which it resembled most are outlined below. That the endocarditis was not a terminal phenomenon is indicated clinically by the appearance of petechiæ early in the disease and pathologically by the presence of extensive fibrosis in the deeper layers of all the endocardial lesions. The abscesses in the left kidney in all probability developed independently of the underlying disease. No purulent foci were found in any of the other internal organs and no staphylococci were found in the vegetations. We interpret the kidney abscesses as metastatic lesions, occasioned by the presence of suppuration in the decubitus ulcers.

The clinical history and postmortem findings of another case belonging to the atypical group will be given briefly to illustrate certain additional manifestations of the disease:

Case II.—E. E. (admission No. 266822), female, aged thirty-seven years, married, was admitted to the Mount Sinai Hospital on January 25, 1923, in the service of Dr. N. E. Brill, to whose kindness we are indebted for the privilege of making this report. Her present illness began nine months before admission with pain, tenderness and swelling of both feet. She was febrile at the time and was obliged to remain in bed for a while. Later, the joint pains became universally distributed and persisted throughout the remainder of her illness. Three weeks before admission she developed chilly sensations, fever, night sweats and cough. She was admitted to the hospital complaining of dyspnea, dysphagia and pain in the throat, all of which had developed during the previous night.

On examination the important findings were fever (temperature, 104.8°) tachycardia, intense dyspnea, an erythematous eruption of butterfly outline over the bridge and sides of the nose extending to the cheeks, resembling acute lupus erythematosus, ulcerative lesions on the lower lip and tongue, purpuric laryngitis, bilateral neuroretinitis, signs of fluid at the left base and enlargement of the liver. The heart was not enlarged; the action was rapid but regular; the sounds were not altered in quality and there were no murmurs. Several days after admission, petechiæ, some of which had white centers, appeared in the conjunctival mucous membrane of both lower lids. The signs of fluid at the left base persisted and signs of consolidation appeared over the right lower lobe. The temperature was constantly elevated, fluctuating between 102° and 104°. The patient grew progressively worse and finally became stuporous and cyanotic, and

died ten days after admission to the hospital. Two days before exitus a friction rub was heard over the left fourth interspace. The blood culture was negative.

At necropsy the heart was found to be somewhat enlarged and there was a patch of pleuropericarditis over the anterior aspect. There were small vegetations on the tricuspid and pulmonary valves. The mitral valve showed diffuse thickening. In the region of the junction of the two cusps, posteriorly, there was a mass of grayish and grayish-pink verrucous vegetations which extended from a point 2 mm. above the closure line to the free edge. There was another group of vegetations on the valve in the region of the junction of the two cusps, anteriorly, where the lesions were flatter. The endocarditic process, which also involved the ventricular aspect of the posterior cusp and the line of attachment of the latter, had spread downward for a short distance along the mural endocardium of the posterior wall of the ventricle. In addition, there were a number of discrete, small areas of mural endocarditis in the right auricle and both ventricles. No bacteria were found in the vegetations.

The right lung was the seat of bronchopneumonia and there was fluid in the left pleural sac. Both lungs showed edema and congestion. The spleen was enlarged, weighing 600 grams.

In this case the pulmonary symptoms dominated the clinical picture and distracted one's attention from the presence of endocarditis. The diagnosis was particularly difficult because of the absence of murmurs and cardiac enlargement. The only definite finding which pointed to infection of the heart valves was the presence of white-centered petechiæ in the conjunctival mucous membrane. The friction rub, which was shown to be due to pleuropericarditis, might have occurred in the absence of endocarditis. The eruption on the face was of the greatest interest, as a similar finding was noted in one other case in our series. The dermatologists were unwilling to identify these lesions as acute lupus erythematosus, but stated that there was a close resemblance. On one occasion we observed similar lesions on the face of a patient who appeared to be suffering from subacute bacterial endocarditis. The patient was being treated in the open air in a cold atmosphere, and it was not possible to state whether or not exposure to the cold and sunlight was responsible for the development of the cutaneous eruption. On the other hand we have never encountered such an eruption in a case of rheumatic endocarditis.

We have had postmortem examinations in 4 cases belonging to the atypical group. The lesions in 2 of the cases have already been described. In all there was involvement of the mitral valve. In 1 instance the vegetations were particularly flat and had a very broad attachment to the valves. The mode of extension of the vegetative process from the mitral valve to the mural endocardium was uniform. In each instance there was involvement of the ventricular aspect of the posterior cusp of the mitral valve as well as of the endocardium at the line of attachment, and from the latter point the vegetations spread downward along the mural endocardium of the posterior wall of the ventricle for a variable distance. In 1 case the vegetative mass extended not only downward toward the posterior papillary muscle, but also forward for a short distance along the interventricular septum. The additional occurrence of isolated patches of mural endocarditis in the right auricle and both ventricles has already been mentioned. Vegetations were found on the tricuspid valve in all the cases. Here the lesions were smaller and flatter and more irregularly distributed than on the mitral valve. In 1 case there was involvement of the endocardium along the line of attachment of one of the cusps. In 2 of the cases the pulmonary valve was involved. In both there were small, irregular, flat vegetations on the ventricular aspect of the valve and, what was more striking, there were also lesions along the line of attachment of two of the cusps. In 2 instances there were small vegetations on the aortic valve. An organizing fibrinous pericarditis was present in all but 1 case. In no instance was the heart greatly enlarged. The spleen showed small infarcts in 3 of the cases and diffuse glomerulonephritis was present in 2.

The microscopic appearance of the endocardial lesions of 1 of the cases was described briefly above. The lesions in the remaining cases were very similar. In all there was endothelial denudation over the greater part of the vegetations. The cellular accumulations in the subendothelial structures consisted chiefly of round cells; in 1 instance, however, the cells were predominatingly polynuclear leukocytes. Evidences of healing were present in all. In each instance the vegetations were free of demonstrable bacteria and the myocardium showed neither Aschoff bodies nor Bracht-Waechter lesions.

The clinical findings in the 4 cases may be summarized as follows: Three of the patients were females and one a male, their ages being ten and a half, nineteen, twenty-four and thirty-seven years respectively. None of the patients complained of any symptoms referable to the heart prior to the onset of the fatal illness. The disease ran a subacute course, lasting from four and a half to nine months. All had fever of irregular type throughout the greater part of the period of observation. Anemia of varying degree was present in all. Blood cultures were uniformly negative. The heart was either normal in size or showed but slight enlargement. All showed tachycardia, and murmurs were heard in all but 1 case (Case II). Three of the patients complained of precordial pain, and in each instance a pericardial friction rub was heard. In Case II the friction rub which was heard was proved at the postmortem examination to be pleuropericardial in origin.

Pulmonary symptoms were present in all. Three of the patients had pleurisy with effusion, and one of these showed in addition outspoken signs of pneumonia. In a fourth patient there were signs of fluid at both bases. She was tapped with negative result, and at autopsy no fluid was found, but the method of examination was inadequate to determine its absence with certainty. Microscopic examination of the lungs, in this case, showed areas of bronchopneumonia.

All the patients showed arthritic symptoms. The joints were not swollen and red as in typical rheumatic arthritis, and presented certain peculiarities which are worthy of mention. It will be recalled that in Case I there was a peculiar discoloration over the metacarpophalangeal joints of the left hand, associated with tenderness but with practically no swelling. In another case some of the joints were swollen and the overlying skin was bluish in color, but there was no pain or tenderness.

Two of the patients had glomerulonephritis. Both had convulsions and died in uremia. A third patient also had convulsions, but no nephritis was found. In all, the urine showed albumin and casts, and in all but one erythrocytes were also present. Apparently there is little or no tendency to leukocytosis in the disease. Repeated examinations showed a leukopenia in 1 of the cases (Case II).

In another case the leukocyte count varied between 6000 and 8400 per cu. mm. The highest count observed was 21,600 (Case I).

The cutaneous manifestations were particularly noteworthy. All the patients showed petechiæ in the skin or conjunctival mucous membrane or both, generally occurring in crops. Many of these petechiæ had white centers. It has already been stated that 2 of the patients showed an erythematous eruption of butterfly distribution on the face which reminded one of acute lupus erythematosus. Erythematous lesions in other parts of the body also occurred. A generalized purpuric eruption associated with erythematous lesions was present in another case. It will be recalled that one of the patients (Case I) developed a localized dermatomyositis early in the disease and later herpes zoster, and that a second patient (Case II) showed ulcerative lesions of the lip and tongue and purpuric laryngitis. Reference has already been made to the occurrence of splenic infarction. In 1 case lesions resembling tender erythematous (Osler) nodes are mentioned in the clinical notes.

Certain of the clinical manifestations, it will be observed, bear a striking resemblance to the symptoms included by Osler in the erythema group. Under the latter designation Osler included a large number of ill-defined and poorly understood cutaneous and visceral manifestations, including certain forms of purpura, angioneurotic edema, erythemas of various sorts, joint symptoms, ulcerative lesions of the skin and mucous membranes, abdominal colic, pericarditis and acute nephritis. Although these varied symptoms were grouped under a single designation a unitary etiology was not hypothecated. It is of interest that Case XXVI of Osler's series[2] showed lesions in the face which resembled acute lupus erythematosus. It is not improbable that a definite relationship exists between the atypical form of endocarditis and certain of the cases included in the erythema group.

For the purposes of differentiation from other types only the rheumatic and subacute bacterial cases need be considered. With these, the disease has certain resemblances, but the dissimilarities are quite striking. The differences in the cardiac lesions, when comparison is made with the rheumatic cases, relate especially to the morphology and localization of the vegetations and to the pres-

ence of Aschoff bodies in the myocardium. In the atypical cases the vegetations have a verrucous character, but tend to be larger and less uniform in size and somewhat more friable than the typical rheumatic lesions, and are attached to the valve by a broader base. Unlike the rheumatic cases the lesions involve the line of attachment of the valves and attack the ventricular and auricular endocardium both by extension from the valves and also in isolated patches. Microscopically the vegetations show more massive superficial thrombus deposit, the cellular reaction is more extensive and more intense and larger areas are denuded of endothelium.

It is significant that none of the 4 cases showed Aschoff bodies in the myocardium. The failure to find these bodies is not conclusive, however, inasmuch as they are frequently absent in rheumatic cases. On the other hand, had Aschoff bodies been found we should have been compelled to classify our cases as rheumatic unless a combined infection could have been demonstrated.

Clinically the differences relate particularly to the manifestations in the skin and mucous membranes and to the occurrence of splenic infarction. We have never seen petechiæ with white centers in a proved case of rheumatic fever. On the other hand, petechiæ both with and without white centers were present in each of our 4 cases. Similarly, erythematous lesions on the face resembling acute lupus erythematosus do not occur in rheumatic fever. Infarction of the spleen is very unusual in rheumatic endocarditis, and when it occurs, generally has its origin not from the vegetations on the heart valves but from a thrombus in the left auricle occurring in association with mitral stenosis.

Positive statements cannot be made at present concerning the significance of the purpura and the glomerulonephritis which occurred several times in the atypical group. Thus far we have not encountered a single instance of generalized purpura or acute nephritis in a case of proved rheumatic endocarditis. The two forms of endocarditis resemble each other in the occurrence of fibrinous pericarditis, the frequency of involvement of the tricuspid valve and the absence of demonstrable organisms from both the vegetations and the blood.

In subacute bacterial endocarditis the vegetations are larger and

more friable than in the atypical cases, and when situated on the mitral valve characteristically spread upward along the postero-lateral wall of the auricle and downward along the chordæ tendineæ. Moreover, involvement of the tricuspid and pulmonary valves is exceedingly uncommon in subacute bacterial endocarditis in the absence of a congenital lesion. Fibrinous pericarditis does not occur except in the presence of some complication or as a terminal event with uremia. Lesions resembling the Osler nodes (tender erythematous nodules) which have hitherto been described only in connection with subacute bacterial endocarditis occurred in one of the cases in the atypical group. In contrast to the latter the vegetations in the active cases of subacute bacterial endocarditis contain large numbers of the characteristic organisms, and the blood cultures are generally positive.

In both forms of endocarditis white-centered petechiæ are found. Whether the lesion on the face in the case of subacute bacterial endocarditis referred to above were identical with those seen in the atypical group cannot be decided definitely. Acute nephritis occurs in both diseases, and in both the spleen may be enlarged. In subacute bacterial endocarditis the so-called Bracht-Waechter lesions are found in the myocardium. These lesions are not specific, however, and cannot be used for differential studies. We have hitherto regarded the focal embolic glomerular lesions described by Loehlein[3] and studied by Baehr[4] as pathognomonic of the subacute cases. Although they were not found in any of the cases in the atypical group, it is conceivable, from a consideration of the character of the vegetations, that the latter may be capable of giving rise to these lesions.

Notes on Etiology, Diagnosis and Prognosis. We have no clue at present concerning the etiologic agent of the disease. It has already been stated that the blood cultures in each instance were negative and that there were no demonstrable organisms in the vegetations. Should the anhemolytic streptococcus be isolated from the blood of an occasional case of the disease it will be necessary to determine whether it is to be regarded as a secondary invader or as indicative of a mixed infection. That the anhemolytic streptococcus is found in the blood of cases of endocarditis in which it is not the

causative agent is borne out by the findings of Swift and Kinsella,[5] who were able to grow the organisms in 8.3 per cent of a series of cases of rheumatic fever. Inasmuch as we do not know the causative agent it cannot be stated with certainty that a unitary etiology obtain for all our cases. It must be left to future studies to determine whether the lesions are due to an undescribed virus or are the extraordinary results of a known etiologic agent.

In view of the limited number of instances of the disease which have been observed, it is obviously unwise to make dogmatic statements concerning the diagnostic value of any one symptom or group of symptoms. The ensuing remarks concerning the diagnosis are based on the assumption that the clinical findings in our cases are the typical manifestations of the disease. The simultaneous occurrence of white-centered petechiæ and fibrinous pericarditis seems to be the most valuable diagnostic finding. This combination of symptoms might be encountered (*a*) in cases of subacute bacterial endocarditis with marked nitrogen retention, where the pericarditis is a terminal event; (*b*) in cases of combined rheumatic and subacute bacterial endocarditis, and (*c*) in the atypical form of verrucous endocarditis. The first of these possibilities is generally easy to determine, for here the nitrogen retention is marked and the pericarditis is a terminal phenomenon. Furthermore, the blood cultures may be positive and the Osler nodes may be found. As for the second possibility, positive blood cultures and the occurrence of the Osler nodes would again indicate the correct diagnosis. In each of the 3 cases of combined rheumatic and active subacute bacterial endocarditis which we have observed the anhemolytic streptococcus was grown from the blood. There remains the third possibility, namely, the atypical form of verrucous endocarditis. It is our impression that the latter form of endocarditis will be found in the great majority of patients showing the combination of white-centered petechiæ, acute pericarditis and negative blood cultures.

The presence of lesions on the face and elsewhere resembling acute lupus erythematosus may prove to have some value for the diagnosis. It is not possible to decide at the present time what significance is to be attached to the occurrence of generalized

purpura, unusual erythematous eruptions, ulcerative lesions on the skin and mucous membranes and dermatomyositis. Acute nephritis seems to be an important finding, but apparently cannot be used for the diagnosis unless it occurs very early in the disease.

In all probability certain cases will be encountered in which the endocarditic manifestations will be masked by other symptoms. Case II is an illustration in point. It will be particularly important in cases of unusual erythematous or purpuric eruptions to search carefully for symptoms pointing to the atypical form of endocarditis.

The ultimate outcome of these cases is a matter of conjecture. The immediate cause of death in our cases was uremia in 2, and pneumonia in the other 2. It is highly probable that mild instances of the disease will be observed, and from a study of such cases it may be possible to determine whether this form of endocarditis is capable of producing chronic valvular defects. Inasmuch as subacute bacterial endocarditis is generally engrafted on diseased valves, it will be important to determine how often the latter disease attacks the valves in cases of atypical verrucous endocarditis. It is quite conceivable that such a superinfection can occur. There is some evidence, both clinically and pathologically, that recurrences develop in the atypical cases. In 3 of the 4 cases there were organic changes in the valves indicative of a previous attack of endocarditis. We have recently had under observation a patient who we believe developed the disease. He had fever, white-centered petechiæ, acute pericarditis, a valvular defect and negative blood cultures. Several weeks after the temperature fell to normal he developed a recurrence of the fever and a fresh crop of white-centered petechiæ appeared. He recovered and now shows only the manifestations of chronic valvular disease. How often a recurrent form and other forms of the disease will be encountered must be left for the future to decide.

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DISCUSSION

Dr. George Blumer, New Haven: Reports of a considerable number of cases of disseminated lupus erythematosus have been published in dermatological literature. In these the disease has frequently terminated in death, with a picture of sepsis. I wondered whether Dr. Libman had looked into these cases reported by the dermatologists to see whether any of them showed the endocardial lesions which he has described.

Dr. L. A. Conner, New York: Is there any clinical picture of cases of this type which have recovered? Did all cases of this kind prove fatal?

Dr. L. F. Barker, Baltimore: I am very much interested in these cases of acute generalized lupus erythematodes. In Baltimore, in Dr. Longcope's Clinic, we have recently had one such case, and Goeckermann in the Mayo Clinic has reported several cases. In some instances, lesions of tuberculosis have been found at autopsy, and it has been thought by some that the whole condition was due to a tuberculous infection; but really only about half the cases have shown tuberculous lesions. I would like to ask Dr. Libman if he thinks that tuberculosis can be regarded as a predisposing factor in some of these cases. It has seemed to me that in acute generalized lupus erythematodes, we must be dealing with some form of general infection (with distribution of the virus through the blood stream) of which the etiological agent is as yet entirely unknown.

Dr. Emanuel Libman (closing): In regard to the questions of Drs. Blumer and Barker regarding acute lupus erythematosus, I do not think that this condition represents as yet a sharply delineated clinical picture. In a number of cases dermatologists will differ, some making a diagnoses of lupus erythematosus and others of some form of erythema. Some of the cases of lupus erythematosus have arthritis involvement, and there are cases of arthritis accompanied by a cutaneous lesion which is clearly not true lupus erythematosus. I have been interested in cases of erythema for over twenty years. There are cases of erythema, resembling lupus erythematosus, accompanied by remarkable visceral and other cutaneous manifestations. At autopsy a verrucous endocarditis was occasionally found. It had, however, the appearance of a terminal endocarditis. The same holds true of postmortem findings in cases of lupus erythematosus. Recently, I carefully studied a paper by Ehrmann, published in the *Archives f. Dermatologie*. It is a most exhaustive study of the subject of lupus erythematosus. I found no record of the occurrence of the type of endocarditis which Dr. Sachs and I have been studying. As regards the relationship of tuberculosis to lupus erythematosus, we have

not found it to be etiological in the cases in which we have had an opportunity of making pathological studies. Tuberculosis may be regarded as one of a number of etiological agents in the disease. It played no role in the causation of the lesions which we have demonstrated today.

In regard to Dr. Conner's question as to the clinical course, one case that probably belongs in the group is alive and doing well. There were two attacks of fever, with pericarditis, white-centered petechiæ and repeatedly negative blood cultures. I believe that the infection can recur, and there is some pathological evidence in support of such a view.

MYOCARDIAL LESIONS

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The observations made by R. C. Cabot, some thirteen years ago, to the effect that the diagnosis in four out of every five cases of chronic myocarditis did not prove correct, and, further, that our knowledge of the lesions associated with angina pectoris left much to be desired, has impelled us to see if the more recent developments in the technic of cardiovascular examination had to any extent clarified our ideas.

With that in view we have compared the clinical and pathological findings of the last 66 cases diagnosed as "primary myocarditis" at the Royal Victoria Hospital. Some of these entered the hospital in a moribund condition and others in a very advanced stage of decompensation, so that a detailed diagnosis was often difficult or impossible, and the designation "myocardial insufficiency" was used; 27 cases of the series showed at autopsy evidences of some form or other of chronic endocarditis, and while in some of these a focal or diffuse myocardial lesion was present, they are all omitted in our investigation. We had, therefore, to deal with 39 cases of so-called "primary myocarditis."

These series have been subdivided into two groups: (1) Cases in which arteriosclerosis was a definite feature, and (2) cases in which there were no definite evidences of disease other than in the myocardium, and cases in which while no myocardial lesions were found there were present the cardinal signs of insufficiency.

Belonging to the arteriosclerotic group there were 24 cases: of

these, 10 showed diffuse fibrosis, 3 had focal lesions only, in 1 the microscopical findings were not reported and 10 were described as free from any primary myocardial lesion of note.

In the second group, of pure myocardial disturbances, there were 15 cases unaccompanied by either arterial sclerosis or endocarditis. It is this group that presents the chief interest. The ages of these patients varied from thirty-five to seventy-six, the average age being sixty years. Of the 15 cases, 8 showed no lesion in the muscle, or at most some faintness of the striæ; 3 showed definite fibrosis and 4 only slight fibroid changes. Of these cases, too, 7 showed normal coronary arteries, 4 had slight change in these vessels, while the remaining 4 manifested definite coronary sclerosis. The relation of this condition to anginal pains is of further interest: In 8 patients there had been decided precordial pains, although only 1 of these had definite lesions of the coronary vessels and 4 were entirely normal.

It will be noted then that myocardial decompensation may occur with very slight evidences of anatomical change; that diffuse lesions are perhaps less common than we suspect and that often there is no sign of myocardial degeneration other than obscurity of the muscle striæ, a change which may or may not be associated with post-mortem or a focal condition. Oftener than not in these cases the nuclear stain was well-preserved, indicating that any existing degeneration was neither marked nor of long duration.

Fatty degeneration, focal rather than diffuse, would seem to be extremely common, but the recent work of Masters renders it possible that we have failed to appreciate the frequent presence of minute fat globules in many hearts that do not otherwise vary much from the normal.

From the clinical point of view there seemed to be really no basis upon which one could make an absolute diagnosis of fibroid myocarditis, nor could one differentiate in most of the cases between fatty degeneration and fibroid change; nor, again, were there clinical signs to suggest from what other anatomical change the muscle has suffered.

In other words, the diagnosis of actual chronic fibroid myocarditis was a matter of inference rather than of accurate differentiation.

In this connection, however, it may be of interest to point out again the frequency of sudden death in lesions at the orifice of the coronary arteries, and in most of these instances syphilis was the etiological factor.

The varied conditions under which decompensation may occur is certainly very striking, the anatomical lesions often being so slight that the disturbed function of the heart muscle cannot always be ascribed to such a cause.

While the detection of myocardial insufficiency is in most instances a matter of ease, there would seem to be a very large group in which the early detection becomes a difficult problem.

The view advocated by Mackenzie, that the myocardium is sound when it does not respond adversely to effort, would seem to be rather too radical to be justified. It must, of course, be admitted that subjective symptoms are more important in this connection than are the objective, and that the history is of more importance than the stethoscope. Nevertheless, many exceptions to the rule occur. I need only refer to such cases of mitral stenosis in women, where the compensation is well-nigh perfect until a protracted pregnancy reveals the inability of the heart muscle to stand the strain; there being, in other words, a functional incapacity which up to that time had not been obvious.

Focal lesions, again, are often so localized and circumscribed as to cause no subjective symptoms provided sufficient healthy myocardium remains to carry on the vascular work without subjective disturbance. Two cases in point illustrate the potential character of this reserve force:

The one, a man, aged thirty-eight years, robust, vigorous and athletic, had no subjective signs of cardiac disturbance until four or five days prior to his death. Then, for the first time, a faintness came over him and a slight oppression in the precordial region. He died suddenly, while sitting at the card-table, and the autopsy revealed the left coronary artery completely occluded at its orifice, while beyond it there was calcification and marked endarteritis. The right coronary artery, while not occluded, was the seat of marked atheromatous changes and small lime deposits. Sections of the heart muscle showed some fatty degeneration, with fragmentation of the fibers.

In the case of another man, aged fifty-two years, active in business and

declaring positively that he had neither subjective nor objective signs of physical incapacity, sudden signs of cardiac collapse developed, and death followed in ten days from a serpiginous perforation of his myocardium. The autopsy revealed an aneurysmal dilatation at the apex of the heart of long standing.

It would seem then that focal lesions may be very serious in their nature and results without giving expression to general insufficiency of the heart.

The detection of insufficiency, indeed, requires the use of every means at our disposal, and no one objective formula will suffice for all cases.

The nature of the diversity of the phenomena which characterize the lessened energy of the heart explains in itself the difficulties in diagnosis. Functional capacity does not depend upon the integrity of the properties of the myocardium alone, nor on its excitability, conductivity, etc. It does depend, however, upon the inherent quality of the muscle, and on its original endowment, as well as upon any possible anatomical change. Function of muscle depends in the main on its power to lengthen out and to recoil, and any fatigue is liable to limit its power to react to impulses.

This reason may, perhaps, explain the fact that the appearance of the muscle alone does not always tell one of its functional capacity. Compensation is a question of dynamics rather than of anatomy. Wiggers has drawn our attention to this interesting fact.

It is a physical attribute of the normal muscle to compensate for any strain, quite irrespective of the presence of hypertrophy, and it is the dynamic function of the heart so to adjust its mechanism that a continuous capillary flow is assured. Only when this fails does decompensation occur.

The determining point of compensation seems to be where the initial tension is relatively too great, so that the pressure maximum diminishes. Following upon this comes the diminution of the systolic discharge.

Thus the initial tension varies not only in different individuals but in the same heart at different times, and so many factors are concerned—physiopathological, mechanical and anatomical—that it does not seem justifiable to attribute myocardial insufficiency to

anatomical changes alone. One must consider the successive depletion and repletion of the cavities, the equilibrium between force and peripheral resistance, vasomotor changes, nervous influence, blood disorders affecting the heart as a whole, the body as a whole, and the centers, as well as to the many other extracardiac conditions which may act adversely on the functioning capacity of muscles in general and heart muscles in particular.

The adaptability of the heart muscle to the varying conditions of the circulation is brought out in an interesting way by Gross. He shows by means of bismuth injections that the functional disturbances of the vascular system in later life are much influenced by changes in the blood supply. With advancing years the relative constitution and construction of the architecture of the heart alters. While before birth there is a right preponderance, and at birth a uniform coronary system, this is gradually shifted in later years to the left side, with relative anemia of the right side of the heart. Accompanying this change there is an increase in the septal anastomosis, with more tortuosity of the vessels. Ample anastomosis of large patent interventricular branches seems to act as part of a safety mechanism. Further, the heart, as a whole, adapts itself to the new circulatory conditions, and so any deviations from the normal vascular supply must affect the nutrition of the heart, the condition of its muscle and its function.

Faulty development of septal anastomosis, or of abundant fat branches after the fourth decade, will materially influence the working capacity and reserve power of the heart. Such hearts are more easily thrown out of balance and exhausted.

It would therefore seem that even in normal hearts in the fifth decade functional disturbances are frequent, and the results of even slight lesions are accentuated.

The problems of the diagnosis of early insufficiency are equally seen in the effort to analyze many of the cases of so-called "irritable heart." Here the symptoms vary so widely (pain, tachycardia, varying blood-pressure, dyspnea, etc.) that a clinical diagnosis of the actual underlying anatomical lesion is often extremely difficult.

F. Müller has emphasized the importance of the nervous system in cardiac pathology:

1. The control of the nervous system on the heart muscle is admitted and the tremendous influence of the vasomotor system in maintaining a normal blood-pressure is of cardinal importance in this connection.

2. As a rule the morbid results of myodegeneration find compensation by vasomotor contractions, and, on the other hand, changes in the vessels find compensation through the altered work of the heart.

3. So many etiological factors come into play—emotion, toxic states, strain, etc.—that the evolution from mere nervous excitability of the heart and vasomotor system to a severe angiosclerosis and impaired myocardium is often impossible to detect.

It is, I think, well recognized that emotional states, if prolonged, lead to structural change not only in the vessels but in the myocardium as well.

Toxic causes, inasmuch as they lead to either temporary or more permanent lesions of the myocardium, help to confuse the diagnosis. Many of these toxic conditions lead to a permanent trouble which may go on for years without ever being fatal.

The effect of strain on the heart is apparently a matter of opinion. For example, as to whether or not acute dilatation can possibly occur with normal muscle. The recent studies of Fahr on chronic myocarditis from hypertension are of interest in this connection.

All the various tests are of use, though in no one of these is the test pathognomonic for all cases. The effort tolerance test, the vital capacity, the oxygen content of the blood, the electrocardiogram, all add their quota to the information, but must be considered only in conjunction with other factors.

The electrocardiogram affords much useful information. In only a few types, however, do the changes in the curve indicate anatomical lesions; much more often do they indicate either fatigue or disturbed function of some sort.

Our observations have inspired the belief that while, in a general way, the normal curve is well recognized, there are, nevertheless, sufficient variations from the normal to cause some hesitancy in the diagnosis. It is, of course, well recognized that a normal electro-

cardiogram is not necessarily indicative of a normal myocardium. We have no better example of this, perhaps, than in the case of a *pulsus alternans*, with which we usually associate a bad prognosis, and which nevertheless presents not infrequently a normal curve.

The amplitude of the *R*–wave is apparently not always proportionate to the energy of the systole, and so we often find the tracing normal.

On the other hand, again, many forms of abnormal curve do not furnish a proof of myocardial disease. In this connection Waller's view is of interest, in which he holds that many other causes relating to volume of one or other portions of the heart, and many extracardiac conditions, may produce deformities of the curve; and among these one must recognize the importance of postural differences in the heart.

Valuable as is the electrocardiogram in telling of many of the deranged functions of the heart, it does not inform us of the type of anatomical lesion, and thus it happens that sometimes we expect too much from this technical method when it fails to show an abnormality which is obvious by other methods of examination.

The prognostic significance of inversion of the *T*-wave in all three leads, for example, has seemed to us of real value, though this view is apparently not shared by everyone. Certain it is, on the other hand, that in not a few of our cases with advanced myocardial disease there was no inversion of the *T*-wave.

In conclusion, I would emphasize the fact that myocardial failure does not necessarily depend on anatomical changes in the structure of the muscle, but that physiopathological conditions may arise sufficient to influence prolonged muscular power of the myocardium and lead to insufficiency.

The means of detecting early insufficiency depends on no single test or device; it calls for every possible factor—the history, the objective physical findings and the technical measures of any and all kinds. By this method only can one in difficult cases determine the real power of the cardiac muscle.

We are indebted to Prof. Oertel for kind permission to use his material.

DISCUSSION

Dr. L. F. Barker, Baltimore: This paper calls to our attention the difficulty in clinical diagnosis in deciding upon the precise pathological and histological changes that underlie observable disturbances of function. Dr. Martin has emphasized the frequency with which a diagnosis of myocarditis is made without justification in many instances. What have been observed are symptoms of "circulatory insufficiency," and the next step is to decide whether these symptoms are due to "myocardial insufficiency" or to "failure of peripheral circulation." When we have decided that we have to deal with myocardial insufficiency, it is often difficult to determine whether the changes in the heart muscle are of inflammatory, of toxic-degenerative or of vascular occlusive origin, and it may be even more difficult to decide as to the exact etiology of such changes. It would seem best to make a "certainty" diagnosis, first, of the functional disturbances and the "probability" diagnosis of the pathological anatomical basis and of the etiology unless the data available justify us in going further.

DIPHTHERIA MYOCARDITIS

(PRELIMINARY REPORT)

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During the last fifty years clinicians have shown a steadily increasing interest in the cardiac manifestations of diphtheria, and are all agreed in opinion as to the very grave significance of the symptoms of cardiac weakness developing during the course of this infection. Cardiac death is at the present time one of the most common forms of fatal termination in diphtheria. In the non-fatal cases irregularity of the heart occurs in 60 per cent of cases (Osler), while murmurs at apex or base are found in 94 per cent. Clinical writers all agree that the chief symptoms of the diphtheria heart are dilatation, irregular rhythm and murmurs. Recent authors have given especial attention to the arrhythmia of diphtheria. Heart-block, auricular and ventricular fibrillation, auricular flutter, extrasystoles, paroxymal tachycardia, etc., have all been observed as features of the cardiac disturbances in diphtheria. As to the gross pathology there is also universal agreement. The common findings are dilatation, softness of the heart-muscle and its "dead-leaf" color. On the other hand, there exists a wide divergence of opinion as to the mechanism of cardiac failure in diphtheria, and as to the microscopic pathology.

The occurrence of fatal cardiac syncope in diphtheria was known at the beginning of the nineteenth century, and the oldest conception of its cause was that of cardiac paralysis. During the first half of the century, cardiac thrombosis with endocarditis and embolism was regarded by many as explaining the sudden deaths

in diphtheria. Bouchut, Eberth, Labadie-Lagrave and others upheld the importance of diphtheria endocarditis. Later it was shown that valvular endocarditis is not common in diphtheria and that it is probable that the agonal clots so commonly found in the heart chambers in fatal cases of diphtheria have been mistaken for true thrombi. Further, the true cardiac thrombi occasionally found in the diphtheria heart are associated with local changes in the endocardium over areas of injured myocardium.

During the seventies the microscopic changes in the heart-muscle began to be noticed and the conception of diphtheria myocarditis began slowly to develop. Oertel found the heart-muscle unaltered in cases dying from suffocation with local symptoms only, but in cases showing general intoxication the myocardium showed hemorrhages, degeneration and accumulations of cells and nuclei between the fibers. In cases dying from sudden paralysis of the heart he noted pale, soft, friable heart-muscle with hemorrhages and advanced fatty degeneration. Wagner found cloudy swelling and fatty change to be the chief pathologic lesions in the diphtheria heart. Hayem and Martin believed that the essential lesion was to be found in the intima of the coronary arteries in the form of an endarteritis which involved the perivascular tissues and ultimately the muscle fibers, the end-result being the development of fibroid patches in the myocardium.

Leyden, in 1882, from a thorough study of the gross and microscopic lesions of the heart in fatal cases of diphtheria, came to the conclusion that the essential cause of the weakness and paralysis of the heart was an "infectious myocarditis." He regarded the changes in the heart muscle as wholly identical with those in the skeletal muscles in typhoid fever and rheumatism, a typical acute myocarditis with intermuscular proliferation of nuclei, fatty degeneration of the fibers, atrophy and pigmentation. He considered the muscle changes as not primary and not proportionate to the myocarditis. Huguenin, 1888, regarded the muscle changes as the cause of the cardiac disturbances in diphtheria. It is worthy of note that he found in the myocardium "myoplastic bodies" similar to those described for the first time, in 1870, by Hayem in the myocardium in typhoid fever. The majority of these

cells showed fatty degeneration. Huguenin also found a proliferating endarteritis of the coronaries, as seen also by Hayem.

The knowledge of the changes in the heart-muscle was greatly advanced by Romberg in 1891. He noted a marked flabbiness of the heart-muscle, with cloudy swelling, fatty, vacuolar and hyaline degenerations, segmentation and anemia. He described in detail the changes in the heart-muscle nuclei. In the heart ganglia he could find no pathologic changes. Hesse believed the primary change to be in the walls of the coronary vessels, followed by leukocyte migration and an interstitial myocarditis. Other writers, as Babes, working with experimental diphtheria, could find no lesions in the thoracic organs.

Veronese, in 1893, introduced a new theory in explanation of the cardiac symptoms of diphtheria. He held that the paralysis of the heart was reflex in origin, as the result of primary degeneration of the sympathetic, particularly of the solar plexus and the celiac ganglion. In reply to this view, Schamschin studied 12 autopsy cases of diphtheria and could find no changes in nerves or ganglia. He concluded that the cause of the cardiac affection in diphtheria was the action of the toxic substance upon the heart-muscle, causing nutritional disturbances followed by structural changes, resulting in altered cardiac function.

The researches of Mosler, Rosenbach, Hayem, Birch-Hirschfeld, Leyden, Romberg and Schamschin established the foundation for the conception of an infectious diphtheria myocarditis. These writers, as well as others of the period, were inclined to the view that the interstitial changes were primary and the muscle changes secondary. Eppinger, however, described a true parenchymatous edema "myolysis cordis diphtherica toxica," as the histologic substratum for postdiphtheritic paralysis of the heart. Thorel was unable to confirm Eppinger's study.

After the discovery of the diphtheria bacillus and its toxin the toxic nature of the cardiac lesions was demonstrated by the experimental works of Welch, Flexner, Comba, Rabot and Philippe, Mollard and Regaut and others. Mollard and Regaut noted hyaline change in the heart-muscle. The conception of an infectious myocarditis was now replaced by that of a toxic myocarditis.

Hibbard found the cause of death in diphtheria to be usually due to cardiac thrombosis, dilatation and paralysis, resulting most probably from the action of the diphtheria toxin.

Since 1900, numerous pathologic studies have been made of the diphtheria heart with contradictory results. Schwenn and others emphasized particularly the fatty degeneration of the heart fibers. Ribbert, in a study based upon 4 cases found fatty degeneration always present but not of essential significance. He considered waxy or hyaline change to be the most important lesion. He found the hyaline muscle to stain reddish with Van Gieson's, while the normal fibers were colorless. He regarded the essential cardiac lesion to be fatty or waxy degeneration of the muscle, followed by an increase of the connective tissue, absorption of the degenerated areas and repair with fibrosis. The interstitial changes are wholly secondary to the muscle injury. There is no primary interstitial myocarditis. He makes no mention of muscle regeneration. Loewenthal studied 34 cases of diphtheria heart by Ribbert's method (Zenker's fixation, hematoxylin and Van Gieson's), but could find no waxy changes in the heart-muscle.

Councilman, Mallory and Pearce in 1901, made an extensive study of 220 fatal cases of diphtheria. They found myocardial degeneration (chiefly fatty degeneration with fragmentation) one of the most frequent lesions in the disease. They describe two kinds of interstitial lesions, one primary and the other secondary to the muscle changes. The second form may lead to fibrosis. Thrombosis due to degeneration or necrosis of the endocardium was not uncommon. Lesions of the coronary vessels played but little part. Regeneration of the heart-muscle was not observed by them. Escherich and others have emphasized the importance of embolism in postdiphtheritic verrucose thrombi in the mitral. Spastic cerebral hemiplegia, due to embolism of the A. fissuræ Sylvii, with infarction, may be confused with postdiphtheritic paralysis.

Cowan discussed the pathologic changes occurring in the heart in acute diseases. With reference to diphtheria, he mentions the observations of Gallaverdin, Mott, Martin and others, who have described fatty change as the most prominent lesion. He, himself, found cloudy swelling to be the most common lesion, while hyaline

changes occasionally occur but are rarely extensive. He regards the changes as due to concentrated toxic action, favored by vascular or other local conditions.

In *Osler and McCrae's Modern Medicine* (1913) the cardiac changes in diphtheria are summed up as consisting essentially of a so-called fatty degeneration, local or general, accompanying or preceding other more advanced forms of degeneration which lead to complete destruction of the muscle fibers. The sarcous elements become swollen, broken up and converted into hyaline masses, with formation of large vacuoles within the cells. No bacteria are found in these areas; they are toxic in origin. Mural thrombi result from the extension of the primary necrosis of the myocardium to the endocardium. Reparative changes lead to the formation of areas of sclerosis. No mention is made of regeneration of the heart-muscle.

Vulfius (1914) and Nuzum (1918) describe eosinophile infiltrations in the heart-muscle in diphtheria. According to the first-named writer they appear about the seventh day of the disease. Nuzum found them in 7 out of 29 cases.

Mackenzie (1918) says of the heart in diphtheria: "The complications here are so varied that danger may arise in several quarters. The heart-muscle itself may be the seat of profound changes, the symptoms somewhat resembling those in rheumatism. But in diphtheria more than in any other acute disease there is a tendency to fatal syncope, and I do not understand how it is brought about."

The very great prominence given in recent years by medical clinicians to studies of cardiac arrhythmia and the pathology of the bundle of His and the heart-regulating system has very naturally given a new turn to clinical and pathologic studies of the diphtheria heart. Nearly every form of arrhythmia has been observed in this condition (paroxysmal tachycardia, auricular and ventricular premature beats, auricular flutter and fibrillation, nodal premature beats, reversal of nodal beats and heart-block). Roentgen-ray and electrocardiographic studies of the diphtheria-heart have been made and attempts made to establish a pathologic basis for the arrhythmia.

Flemming and Kennedy (1910) studied the pathologic changes in a case of complete heart-block in diphtheria. The auriculoventricular node and first part of the auriculoventricular bundle as well as the ventricular muscle showed an acute inflammation. The vagi were found to be normal. Price and Mackenzie (1911) found extreme degeneration and cellular infiltration of the myocardium in a case of auricular fibrillation and heart-block in diphtheria. The sinoauricular node and bundle were not involved. No changes were found in the nerve-trunks or ganglia. Rohmer (1912) saw cases which lead him to believe that the toxin of diphtheria has no especial affinity for the conducting system. Tanaka (1912) also thought that lesions of the conducting system are rarely the cause of cardiac death in diphtheria. In 14 out of 15 cases dying in cardiac syncope fatty degeneration of the myocardium was present; in 6 of these cases interstitial inflammatory changes were present. Hecht (1913) found fatty degeneration, cloudy swelling and interstitial round-cell infiltrations in the myocardium. Hume and Clegg (1914 to 1915) found fatty change in the muscle of both ventricles, congestion and hemorrhage with round-cell infiltration of the sinoauricular node, while the auriculoventricular node showed only congested capillaries. Fahr (1920) found areas of waxy degeneration in the bundle of His in a case of heart-block. In another case round-cell infiltration of the sinoauricular node and the bundle of His were seen. In 2 other cases there was no involvement of the bundle although a wide-spread degeneration of the myocardium was present. In another case with fatty change and a definite myocarditis the bundle was not involved.

Aviragnet, Lutenbacher and Soudier (1918 to 1920) found definite lesions in the bundle of His and believe that the toxin of diphtheria has an especial affinity for it. Most of the fibers of the myocardium were altered, showing atrophy, tumefaction, vacuolation and loss of striation. The nuclei were pale, deformed, often showing karyolysis. No fatty change was seen and no fibrosis. The interstitial lesions were characterized by edema, mononuclear infiltration, fibroblasts and myoblastic bodies. These changes were diffuse, but especially marked in the bundle of His and its neighborhood.

In an electrocardiographic study of 80 cases of diphtheria, McCulloch (1920) found 19 showing evidence of myocarditis and he regards diphtheria myocarditis as having a definite position among those factors that lead to chronic heart disease later in life.

Friedemann (1921) states that he formerly held the view that the muscle changes in the heart in diphtheria were secondary to a loss of tone following paralysis of the sympathetic and ganglia. This view he regards as no longer tenable. The direct injection of adrenalin into a dilated heart in diphtheria caused contraction of the heart, the pulse went to 140, but later the heart dilated again and death took place.

Bie and Schwensen (1922) treated 2 cases of diphtheria arrhythmia with digitalis. One patient recovered; the other died from progressive acute myocarditis, which attacked the atrioventricular bundle and caused partial heart-block.

Schwensen (1922) regards diphtheria as an important cause of cardiac insufficiency later in life. One patient examined two years after an attack showed cardiac impairment. He examined the hearts of 568 cases of diphtheria, 118 of which were severe and 8 were fatal cases. Clinical signs of acute myocarditis were found in 17 per cent of the 568 cases and in 75 per cent of the grave cases and in all of the fatal ones. Two kinds of arrhythmia were noted: (1) Organic heart-block with pallor, syncope, cool skin and death early in the disease; (2) extrasystoles occurring late (thirty-three days) without death. In 4 cases of the first type the histologic examination showed the same changes in the atrioventricular node and bundle of His as in the myocardium.

The above brief review of the more important literature on the heart in diphtheria shows the unsatisfactory and unsettled state of our knowledge of its pathology and the relation of the latter to the clinical phenomena. Fatty degeneration, cloudy swelling, hyaline degeneration or necrosis, vacuolization and segmentation of the heart-muscle, with or without evidences of inflammatory reaction and repair, have been regarded by individual observers as the essential lesion of the myocardium or its conducting system,

or of both. Other writers regard the myocardial changes as secondary, and explain the cardiac failure as the result of disturbances in the sympathetic nerves and ganglia or in the peripheral vasomotor system.

There is presented here a pathologic study of the hearts in 16 autopsy cases of fatal diphtheria: 15 of these cases were furnished by the University Hospital, and the autopsies made in the Pathologic Laboratory of the University of Michigan. Of these 15 cases, 1 was from the Clinic of Internal Medicine (Dr. Dock), 5 from Otology (Dr. Canfield), 1 from Orthopedic Surgery (Dr. Abbott), 8 from Pediatrics, and all but 1 case coming from the Contagious Ward (Dr. Cowie). The material of the sixteenth case was received from Dr. L. Hektoen, of Chicago. The cases are considered chronologically.

The method of study was the same for each of the 15 cases autopsied by us. The gross pathology of the heart was noted at autopsy. Blocks were taken from both auricles and ventricles, including portions of the septum and apex. Paraffin imbedding was employed and the sections stained with hematoxylin and eosin, methylene blue and eosin and Van Gieson's. Frozen sections were used for the fat-dyes, Sudan III, Scharlach R. and Nile-blue sulphate.

Case I.—Autopsy 119. H., male, aged twenty-five years; laborer. (Internal Medicine.) Had been ill for three days with sore throat, diagnosed as quinsy, entered the hospital on the evening of December 11, 1902. Marked cardiac dilatation, irregularity and tachycardia. Tonsils and pharynx covered with diphtheritic membrane. Cardiac symptoms grew rapidly worse and death from cardiac syncope took place at one o'clock that night.

Heart. Macroscopic: Both ventricles and auricles dilated; flabby; flattens on board; muscle very soft; translucent, tears easily, pale brownish-yellow. Large agonal clots in both ventricles. No changes in valves or coronary vessels.

Microscopic: Heart-muscle fibers small, atrophic. Marked congestion of the bloodvessels. Numerous minute hemorrhages scattered through the myocardium. Perivascular edema. Increase of leukocytes in bloodvessels. Slight small-celled infiltration around some of the veins (*early myocarditis*). Muscle shows scattered areas of fatty degenerative infiltration, particularly beneath the endocardium. Many fibers show hyaline

change with loss of striation and staining power. Other fibers show marked cloudy swelling, even to necrosis. Majority of nuclei are pyknotic. Some fibers show advanced Zenker's necrosis with irregular clear spaces in the muscle substance. Endocardium and pericardium are edematous. Pharyngeal striped muscles show extreme Zenker's necrosis.

Other organs showed extreme congestion; general edema; slight fatty degenerative infiltration of liver; cloudy swelling of kidneys; lymphocyte destruction in spleen with coagulation necrosis of centers of splenic follicles; numerous bone-marrow giant-cells in pulmonary and liver capillaries; extensive diphtheritic membrane in tonsils, palate and pharynx, extending into larynx; Klebs-Loeffler positive.

Case II.—Autopsy 456. W., male, aged forty years, farmer. (Otology and Contagious Ward.) Diphtheria of pharynx and nose developed on February 23, 1914. Cultures positive Klebs-Loeffler. 10,000 units given. On March 7, 1914, showed dilated heart, with marked irregularity and tachycardia. Temperature, 103°.

Heart. Macroscopic: Pericardial sac contained an increased amount of fluid, of deep yellow color and containing numerous white flaky coagula. Epicardium smooth and clear, vessels markedly congested. Heart twice as large as cadaver's fist, filled with soft cruor. All cavities of heart markedly dilated. Ventricular walls thin. Muscle soft, brownish in color.

Microscopic: Myocardium, especially of left ventricle, shows extreme Zenker's necrosis with areas of partial absorption of the dead muscle, fibroblastic proliferation and muscle regeneration. The dead muscle appears as if cooked, waxy, of yellowish color and staining poorly with eosin. In areas around the veins the muscle fibers show large irregular vacuoles as in advanced Zenker's necrosis. The lining muscle in these areas shows myoblastic proliferation with the development of sarcoplastic fibrillæ extending into the dead muscle. The fat content is slight. In the neighborhood of the proliferating muscle there is lymphocyte infiltration and fibroblastic infiltration. The vessels show extreme congestion and perivascular edema. The microscopic picture is that of a severe parenchymatous myocarditis with beginning inflammation and repair. Sections of the bundle of His showed similar changes, but with more marked edema and hydropic degeneration.

Other organs showed marked congestion; cloudy swelling of liver and kidneys; early bronchopneumonia; lipoidosis of intima of aorta and deficiency of colloid in the thyroid. Pharyngeal muscles showed marked Zenker's necrosis with interstitial inflammatory reaction.

Case III.—Autopsy 479. G. C., male, aged three years. (Pediatrics.) Had had diphtheria on May 30, 1914. Two weeks after recovery developed difficulty in speaking and swallowing, followed by general muscular weak-

ness. Entered hospital on July 15, 1914. Could not lift head, due to weakness of muscles of back. Could not support himself on legs. No marked wasting. No toe-drop. Patellar reflexes lost. Paralysis of soft palate. Temperature, 99.6°; pulse, 122; first sound at apex soft. Died suddenly of cardiac failure on July 17, 1914.

Heart. Macroscopic: Heart greatly enlarged, particularly the right side, with marked separation of the muscle fibers. Slight thickening of pericardium on anterior wall of right ventricle. All cavities dilated, especially right heart. Filled with fluid blood except right auricular appendage, which contains cruor. Left ventricular wall averages 14 mm. in thickness; right, 4 mm. Valvular orifices dilated; flaps negative. Vessels negative. Myocardium slightly paler than normal and distinctly clouded. Soft and tears easily.

Microscopic: Muscle fibers show diffuse slight hyaline change with patches of more marked waxy necrosis. In the fibers showing the slight change, there is a loss of striation and staining affinity for eosin; the fibers are more highly refractive. In the advanced areas the fibers are yellowish and have lost their nuclei. Areas of marked fatty degenerative infiltration are also present, especially in the neighborhood of the endocardium. Some of the papillary muscles show extreme fatty change. No inflammatory reaction and no evidences of repair.

Other organs: Thymicolymphatic constitution; right testis not descended; early bronchopneumonia; passive congestion of all organs; slight fatty change in liver; slight cloudy swelling of kidneys.

Case IV.—Autopsy 516. C. L. F., male, aged two years. (Otology and Pediatrics.) Admitted April 23, 1915. Had supposedly aspirated a peanut on the day before. Had paroxysms of coughing, but peanut was not recovered. Followed by alternate periods of dyspnea and quiet. Patient was cyanotic at one time for a few minutes. Roentgen-ray examination showed bilateral emphysema, but no foreign body seen. Attempted removal by bronchoscopy. Apparent foreign body seen in trachea, but attempts to remove it were unsuccessful. Thymus was much enlarged, and it was thought that the tracheal obstruction might be due to that. On April 24, 1915, tracheotomy was performed and tube inserted. Portion of peanut removed from right main bronchus. Followed by slight temperature, cyanosis and labored breathing. On the following day evidences of bronchopneumonia. Temperature, 104.2°; on the following day, 103.2°. Patient became cyanotic; pulse, 145, very irregular; heart dilated on right; respirations shallow. Clinical diagnosis of membranous bronchitis. Died of cardiac failure on May 5, 1915.

Heart. Macroscopic: Enlarged, especially on right side. All cavities dilated. Contained agonal clots. Heart-muscle yellowish, with fatty shine, translucent, moist, soft and easily torn. Valves and vessels negative.

Microscopic: Early hyaline change. Portions of the fibers are waxy, stain poorly with eosin and show pyknotic nuclei. Striation is lost. The unaffected portions of the fibers stain well with eosin. Fat content normal. Vessels congested. No inflammatory reaction. No evidences of repair.

Other organs showed extensive necrotic diphtheritic membrane involving tonsils, pharynx, larynx, trachea and main bronchi; aspiration bronchopneumonia with beginning gangrene; marked fatty degenerative infiltration of liver and acute passive congestion of all organs. Bacteriologic examination of membrane showed pure cultures of Klebs-Loeffler bacilli.

Case V.—Autopsy 664. C. H. T., aged thirty-one years. (Contagious Ward.) Entered November 24, 1916 with sore throat. On November 27, transferred to Contagious Ward. Membrane on both tonsils. Cultures positive. 10,000 units given intravenously; 10,000 units intramuscularly, but without effects. 10,000 more given. On November 28 membrane covered both tonsils, uvula and pharyngeal wall. Very toxic, delirious. Temperature, 103°; pulse, 142, very irregular. Respirations very labored. Died on the following day in cardiac syncope.

Heart. Macroscopic: Left heart in firm rigor. Right side dilated. Heart-muscle pale, yellowish-brown, especially beneath endocardium. Valves and muscles negative.

Macroscopic: Diffuse cloudy swelling. Fibers have lost their striation and stain more heavily with eosin. Nuclei pyknotic. Patches of marked waxy necrosis in which the fibers are waxy, yellowish and take but little or no eosin. Fat content not increased. Vessels congested. Interstitial tissue edematous. No inflammatory reaction and no evidences of repair.

Other organs showed diphtheritic membrane on tonsils, palate, pharynx, larynx, trachea and bronchi; multiple hemorrhages and hemorrhagic infarctions of lungs; Zenker's necrosis of pharyngeal muscles; passive congestion and cloudy swelling of all organs; chronic orchitis; periadrenalitis, peripancreatitis and pancreatitis, probably syphilitic; colloid goiter; tattoo.

Case VI.—Autopsy 720. E. S., female, aged two and a half years. (Pediatrics and Contagious Ward.) Two weeks before admission had developed difficult respiration and inability to talk, with cyanosis. No history of aspiration of foreign body. No preëxisting infection. Roentgen-ray examination thought to indicate presence of foreign body. Tracheotomy. No foreign body seen. Mass occluding trachea just above bifurcation thought to be enlarged thymus. After operation temperature ran 100 to 103.5°; pulse, 110 to 130, very irregular; respiration, 40 to 48, attacks of coughing with thick yellow sputum. Convulsions. Died of cardiac failure April 23, 1917.

Heart. Macroscopic: Approximately normal in size; left side in rigor; right side dilated and filled with soft cruor. Heart-muscle yellowish,

especially beneath endocardium. Cloudy areas. Soft. Valves and vessels negative.

Microscopic: Diffuse hyaline change most marked in left ventricle and septum. Fibers homogeneous, stain poorly, striation lost, and nuclei slightly pyknotic. A few fibers show cloudy swelling. No fatty change. No inflammatory reaction, and no evidence of repair or regeneration.

Other organs showed diphtheritic tonsillitis, pharyngitis and laryngitis (Klebs-Loeffler); streptococcus infection of tracheotomy wound; acute purulent bronchopenumonia; acute passive congestion and parenchymatous degeneration of all organs; thymicolymphatic constitution.

Case VII.—Autopsy 732. W. V. F., male, aged three years. (Otology and Contagious Ward.) Referred from Otology, May 6, 1917, because of croupy cough. Had been operated upon for mastoid infection. Laryngeal diphtheria. 10,000 units given. No effect. Tracheotomy. Death from cardiac syncope during the night.

Heart. Macroscopic: Right side dilated. Heart-muscle yellowish-brown. Soft. Translucent.

Microscopic: Diffuse hyaline change. Muscle fibers homogeneous with loss of striations and light staining with eosin. Only occasional fibers show fat droplets. No inflammatory reaction and no evidence of repair or regeneration. Bloodvessels congested.

Other organs showed interstitial emphysema of mediastinal tissues extending from tracheotomy wound; diphtheria of larynx and trachea; phlegmonous infiltration of thyroid and cervical region; acute catarrhal bronchitis; chronic mastoiditis with operation; congenital syphilis (white pneumonia, miliary gummas); lymphoid hyperplasia; atrophy of thymus; cloudy swelling of liver and kidneys; general passive congestion.

Case VIII.—Autopsy 796. Mrs. S. V. M., aged eighteen years. (Contagious Ward.) Had sore throat February 11, 1918. Mild delirium. Very toxic. Coughed up membrane on March 1, 1918. Positive Klebs-Loeffler. 20,000 units given intravenously, 10,000 subpectorally. Temperature, 102.3°. Developed laryngeal extension. 10,000 units intravenously on March 2. On March 3, partial paralysis of right arm and leg. Reflexes lost on right side. 10,000 units more given. On March 4, temperature 104.6°; cyanosis marked, respirations very difficult and rapid; pulse 200, very irregular. Total loss of reflexes and knee-jerks. Death in cardiac syncope, March 4, 1918.

Heart. Macroscopic: About normal size. Muscle dark reddish-brown, slightly more friable than normal. Cloudy. No fatty change visible to naked eye. Valves and vessels negative.

Microscopic: Diffuse hyaline change and cloudy swelling. No complete

necrosis. Slight fatty degenerative change beneath endocardium. Congestion of vessels. Localized areas of fibrosis. Healed myocarditis.

Other organs showed diphtheria of tonsils, uvula, tongue, epiglottis and pharynx; thrombosis of right jugular vein with multiple pulmonary emboli; acute purulent bronchopneumonia; general passive congestion; cloudy swelling of kidneys.

Case IX.—Autopsy 984. M. S., male, aged six years. (Pediatrics.) On December 11, 1919, showed positive cultures of Klebs-Loeffler. Had had "tonsillitis" four days before. Bloody discharge from nose. Septic temperature. 6000 units given, followed by 10,000 on the day following. Involuntary micturition. Temperature, 99 to 100°; pulse, 120 to 130, irregular; respirations, 30 to 60. Became very toxic. Hematuria. Constant vomiting. Paralysis of bladder. Delirium. Marked irregularity of pulse. Died in cardiac syncope, December 26, 1919.

Heart. Macroscopic: Slightly enlarged. Slight fatty degenerative infiltration beneath endocardium. Valves and vessels negative.

Microscopic: Marked diffuse hyaline change of muscle fibers, more severe in left ventricle than in right. Papillary muscles show marked fatty degenerative infiltration. Vessels congested. No inflammatory reaction and no evidences of repair or regeneration. No complete necrosis.

Other organs showed diphtheria of tongue, pharynx and esophagus; purulent cystitis, ureteritis and pyelonephritis; multiple abscesses of kidneys; purulent bronchopneumonia; passive congestion and cloudy swelling of all organs; monorchidism.

Case X.—Autopsy 990. B. B., male, aged twenty-two years. (Contagious Ward.) Right kidney had been removed six months previously. Developed erysipelas. On January 7, 1920, patchy membrane developed in right tonsil; on January 9 had spread over pharynx, with well-defined cervical cellulitis. Positive K. L. 20,000 units were given intravenously and 20,000 intramuscularly. Became very toxic; temperature, 103°; pulse, 130 to 201, very irregular; respirations, 30 to 40; casts and albumin in urine. Died of cardiac failure, January 11, 1920.

Heart. Macroscopic: Heart slightly enlarged. Walls thin, atrophic. Heart-muscle yellowish-brown, cloudy, soft. Valves and vessels negative. Early lipoidosis of intima of aorta.

Microscopic: Marked hyaline change and early necrosis. No cloudy swelling. No fatty change. Vessels congested. No inflammatory reaction. No evidence of degeneration or repair.

Other organs showed diphtheria of pharynx; chronic tuberculosis of bladder, prostate, seminal vesicles and bronchial nodes; miliary tubercles in lungs, spleen, liver, kidney, tonsils, prostate, peritoneum and pancreas; atrophic arthritis; erysipelas; cervical cellulitis; general passive congestion and cloudy swelling of all organs.

Case XI.—Autopsy 1135. W. M., male, aged thirteen years. (Pediatrics.) History of congenital syphilis. Had had diphtheria three weeks before coming to hospital. Complained of pain in right side, shortness of breath and cough. No membrane in throat. Pulse, 90. Became rapidly worse and increasing cyanosis, blood-streaked sputum, Cheyne-Stokes respiration, pulse, 130 to 150; temperature, 99 to 101°. Pulse at times regular; at other times very irregular. Apex outside of nipple line. No murmurs or thrills. Died, March 24, 1921. Clinical diagnosis of bilateral pneumonia.

Heart. Macroscopic: Greatly enlarged and dilated. Weight, 410 grams; measures 12.5 x 12.5 x 5.5 cm. Apex slightly bifid. All cavities and valvular orifices dilated. Ventricular walls thin. Polypoid parietal thrombus in left ventricle near the apex. Muscle yellowish-brown, particularly toward the apex. Soft.

Microscopic: Diffuse hyaline change with patches of waxy necrosis in wall of left ventricle. Near the endocardium many fibers show marked fatty degenerative infiltration. Parietal thrombus over this area. Throughout the myocardium individual fibers show advanced Zenker's necrosis and marked vacuolation. Partly disintegrated fibers appear here and there. About these edema of the interstitial substance, lymphocyte infiltration and early fibroblastic proliferation. Early myocarditis and repair. Vessels congested. Interstitial tissues edematous. In the areas showing necrotic portions of fibers, the living portions show large hypertrophic and hyperchromatic nuclei. Early muscle regeneration. Sections of bundle of His showed marked vacuolation of the fibers, congestion and edema.

Other organs showed hyperplastic tonsillitis with diphtheritic patches in crypts; multiple anemic infarctions of kidneys and hemorrhagic infarctions of lungs; bronchopneumonia; marked passive congestion of all organs; thymicolymphatic constitution; duplication of left ureter; ascites.

Case XII.—Autopsy, 1178. W. Z., male, aged fourteen years. (Contagious Ward.) Two weeks before admission had had sore throat and slight fever diagnosed as tonsillitis. Two days ago became worse. Throat very sore; great difficulty in speaking; regurgitation of food through nose. Extensive dirty-gray membrane on both tonsils and soft palate. Heart sounds very rapid, otherwise good. 10,000 units given intravenously, 40,000 intramuscularly. Very slight reaction. Temperature, 101 to 102°; pulse, 100 to 110; respirations, 30. Became increasingly toxic, delirious. Intubated. On the next day comatose; temperature, 105°; pulse, 160; death in cardiac syncope, June 22, 1921.

Heart. Macroscopic: Not enlarged. Rigor. Right side not dilated. Numerous minute petechial hemorrhages beneath epicardium. Muscle pale on section. Valves and vessels negative.

Microscopic: Early hyaline change and cloudy swelling. Slight fatty degenerative infiltration. Congestion of bloodvessels. No inflammatory reaction. No repair or regeneration.

Other organs showed diphtheria of tonsils, larynx, pharynx, trachea and large bronchi; acute bronchopneumonia; multiple subserous hemorrhages; asphyxia; passive congestion and parenchymatous degeneration of all organs. Thymicolymphatic constitution.

Case XIII.—Autopsy 1225. W. H., male, aged four years. (Otology and Contagious Ward.) K. L. infection following removal of aspirated peanut. On November 23, 1921, tracheotomy, with removal of peanut from bifurcation. Child was extremely cyanotic, revived with difficulty. Condition improved after operation. Five days later respiratory difficulty suddenly increased. Large pieces of membrane were removed from trachea and bronchi. Bacteriologic examination showed pure culture of K. L. bacilli. Admitted to Contagious Ward. Direct smear from membranes showed countless numbers of K. L. bacilli. 25,000 units given intravenously; 15,000 more intramuscularly. Child quickly became very toxic, and cyanotic. 20,000 units more given intravenously and 20,000 more intramuscularly. Bronchial cast coughed up, a pure culture of bacilli. Pulse, 120 to 140, very irregular; temperature, 100 to 102°; respirations, 35 to 40. Died in cardiac syncope, November 28, 1922.

Heart. Macroscopic: Dilatation of all cavities. Heart-muscle, yellowish-brown, translucent, soft, tearing easily. Marked tiger-heart. Valves and vessels negative.

Microscopic: Marked fatty degenerative infiltration and hyaline change. Fatty change most marked in left ventricle near the endocardium. Marked tiger-heart. Marked congestion of vessels. No inflammatory reaction. No repair.

Other organs showed aspiration pneumonia in right lung; tracheal and bronchial diphtheria; interstitial emphysema of left lung. Diffuse inflammation of peritracheal and mediastinal tissues. Lymphatic constitution. Passive congestion and parenchymatous degeneration of all organs. Meckel's diverticulum.

Case XIV.—Autopsy 1388. H. D., female, aged seven years. (Contagious Ward.) Entered with diagnosis of diphtheria. Had been ill for two days. Very toxic. Cervical glands enlarged. Membrane in pharynx. Given 10,000 units intravenously and 40,000 in buttocks. Immediately had severe chill, stridulent respiration, extremities stiff, involuntary expulsion of feces. Became very restless and cyanotic, and died within fifteen minutes; adrenalin injection of no avail.

Heart. Macroscopic: Moderately dilated. Rigor mortis contraction. Muscle apparently normal.

Microscopic: All of the muscle fibers show a more or less marked hyaline appearance with pyknosis and fragmentation of many of the nuclei, although the chromatin is not completely lost anywhere. Early Zenker's necrosis. Striations lost. Very few minute fat droplets.

Other organs showed tonsillar diphtheria; hyaline necrosis of striped muscles of pharynx and larynx; thymicolymphatic constitution; parenchymatous hypertrophy of thyroid; marked congestion of lungs with multiple hemorrhages; acute catarrhal laryngitis, tracheitis and bronchitis. Old tubercles in lungs and bronchial nodes. Oxyurids in appendix.

Case XV.—Autopsy 1398. R. L., male, aged two and a half years. (Otology and Pediatrics.) Had laryngeal papilloma removed in Otology Ward with tracheotomy. Diagnosis of diphtheria on December 15, 1922. 20,000 units given intravenously and 20,000 intramuscularly. One hour later temperature rose rapidly to 107°. Developed marked dyspnea, epileptiform convulsions; in the second hour pulmonary edema and convulsions became more severe. Six hours after injections child stiffened and died. Adrenalin of no effect. Heart not examined during this period. At entrance was negative. K. L. positive.

Heart. Macroscopic: Dilated. Small petechial hemorrhages beneath the endocardium. Yellowish-brown in color. No fatty change visible to naked eye. Valves and vessels negative.

Microscopic: Diffuse early hyaline change. Subepicardial fatty change in right ventricle. Congestion of vessels. No inflammatory reaction. No repair.

Other organs showed diphtheria of tonsils and trachea; thymicolymphatic constitution; miliary tubercles in bronchial and mesenteric nodes; older tuberculous focus in base of right lung; recurrent laryngeal papilloma with tracheotomy; localized hypertrophy of thyroid; marked congestion, edema and multiple hemorrhages in lungs; passive congestion and parenchymatous degeneration of all organs.

Case XVI.—Material received from Dr. Ludwig Hektoen, of Chicago. Male child, two years old, died two days after admission to hospital. Three days before had been taken ill with sore throat and vomiting. No physician called until the third day, when 20,000 units were given and the child taken to the hospital, where 20,000 units more were given. Tonsils were large and covered with membrane which extended over uvula and posterior pharyngeal wall. On the day after admission the pulse became slow, weak and irregular, and remained irregular in spite of hypodermic injections of caffein and application of heat externally. Heart-beats were skipped and there were premature contractions. Death occurred on the sixth day of illness. Autopsy showed changes only in the throat, heart and lymphoid tissue of the intestinal tract, as follows: Diphtheria of throat,

with some edema of the epiglottis; pale, flabby and friable myocardium; heart weighed 70 grams; there was hyperplasia of the lymphoid tissues of the intestinal tract. There was no pneumonia.

Microscopic: Sections of the myocardium showed an intense diffuse hyaline change. The muscle fibers were swollen, hyaline, homogeneous, with loss of striation and staining power. The nuclei were deformed and pyknotic and in the most hyaline portions of the fibers completely lost. Occasional fibers showed cloudy swelling, staining heavily with eosin. Very few fat droplets. In the middle layer of the left ventricle the parenchymatous changes were most marked. Portions of the fibers showed complete hyaline necrosis, the interstitial tissue about such fibers was edematous and showed early lymphocyte infiltration and fibroblastic proliferation (early myocarditis). No regeneration of cardiac muscle. The portions of the bundle of His included in the blocks taken showed the same changes as in the other portions of the myocardium.

Summary of Cases. The ages of the patients were 25, 40, 3, 2, 31, 2½, 3, 18, 6, 22, 13, 14, 4, 7, 2½ and 2 years.

The duration of the infection varied approximately as follows: 1 to 2, 2 to 3, 4, 6, 12, 14, 15 and 16 days, and 2½, 3 and 6 weeks.

It is of interest that two of the cases developed after the removal of an aspirated peanut. They were both characterized by the severity of the diphtheritic tracheitis and bronchitis which extended into the smaller bronchioles, and by the virulence of the organisms, as shown by the enormous numbers of Klebs-Loeffler bacilli in the membranes. In both cases the nature of the bacilli present was demonstrated bacteriologically. In a third case from the Otology Ward the child had had a previous tracheotomy for recurrent papilloma of the larynx. It would appear from these cases that the mechanical trauma caused by such operations favors the development of diphtheria either from bacilli carried by the patient or received after the operation. In a fourth case sent from the Otology Ward with supposed foreign-body obstruction no foreign body could be found on examination or at autopsy, and it is most probable that this case was one of diphtheria from the beginning.

Two of the cases died following the administration of antitoxin. Both children showed well-marked features of the thymicolymphatic constitution with areas of parenchymatous hypertrophy in the thyroid resembling that of exophthalmic goiter. The pathologic

picture of anaphylactic death was not shown by these cases. No characteristic increase in the distribution of leukocytes in the hepatic capillaries was present. We regard the death in these cases as the result of the combination of diphtheria and the thymicolymphatic heart, the antitoxin injections serving as any other exciting factor (burns, cold, emotion, etc.) to bring about the cardiac form of death.

All of the 16 patients died a cardiac death. Disturbances in rate, rhythm and heart sounds were present in all, with a general picture of dilatation. The emergency character of many of the cases prevented any especial cardiac study clinically, and none was attempted. Nevertheless the clinical impression received from each case was that it was one of "cardiac failure." The autopsy findings bear this out. In every case there was more or less marked cardiac dilatation, involving all of the heart chambers, or especially marked on the right side.

No endocarditis was seen in any one of the cases.

In one case only there was a mural thrombus. This was situated in the left ventricle near the apex, over an area of severely damaged myocardium, the degeneration and necrosis extending to theendocardium. In one case there was a thrombosis of the right jugular vein with multiple pulmonary embolism.

It is a striking fact that nine of the cases presented well-marked features of the thymicolymphatic constitution, again an emphasis of the liability of this constitution to death from acute infections.

In nine of the cases there was a more or less pronounced bronchopneumonia present. In the rapidly developing cases with early death pneumonia was absent or agonal; in the more severe and prolonged cases, and in those with aspiration, it was more marked. The cardiac embarrassment was no doubt increased in these latter cases, but it is important to note that the cardiac symptoms may be as pronounced in the cases without pneumonia as in those with it.

The general pathology of the cases, besides those mentioned above, consisted of a generalized passive congestion, often with petechial hemorrhages, especially marked in lungs, parenchymatous degeneration of liver and kidneys (cloudy swelling or degenerative

fatty infiltration) and lymphocyte exhaustion of germ centers of spleen and lymph nodes. In those cases in which they were examined the striped muscle fibers of the pharyngeal and laryngeal muscles showed a marked Zenker's necrosis.

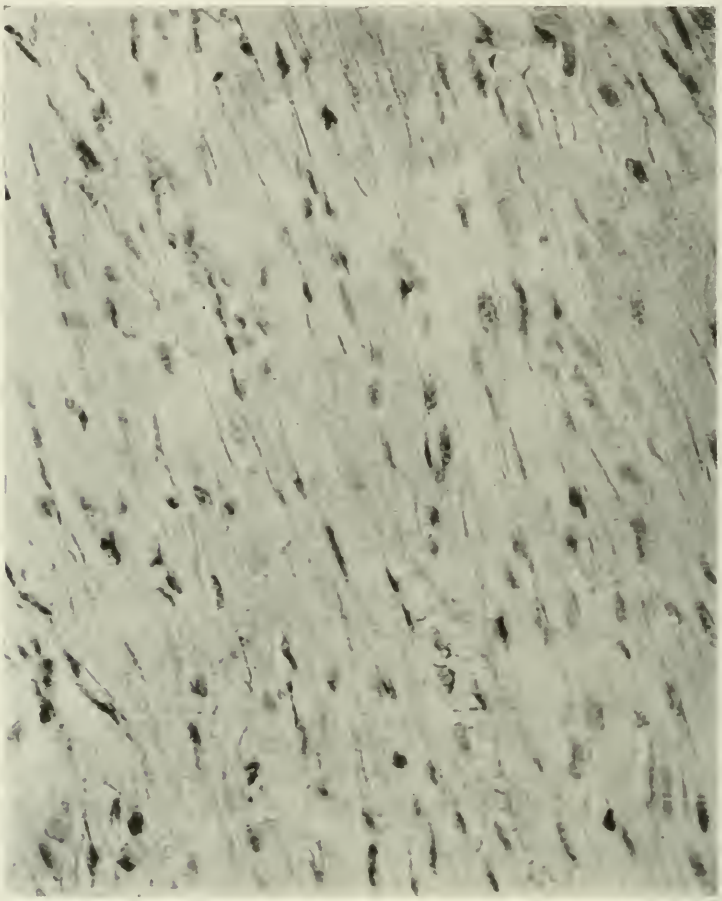

FIG. 1.—Myocardium from Case VII, two to three days' duration. Diffuse hyaline degeneration and necrosis. No inflammatory reaction.

The essential pathologic lesion, aside from the local diphtheria process, in every one of the cases is a *marked parenchymatous degeneration of the heart-muscle.*

In every case hyaline degeneration or necrosis was present. This is the one constant parenchymatous lesion. In the early deaths this may be the only histologic lesion in the myocardium. It is characterized by more or less tumefaction with loss of striation

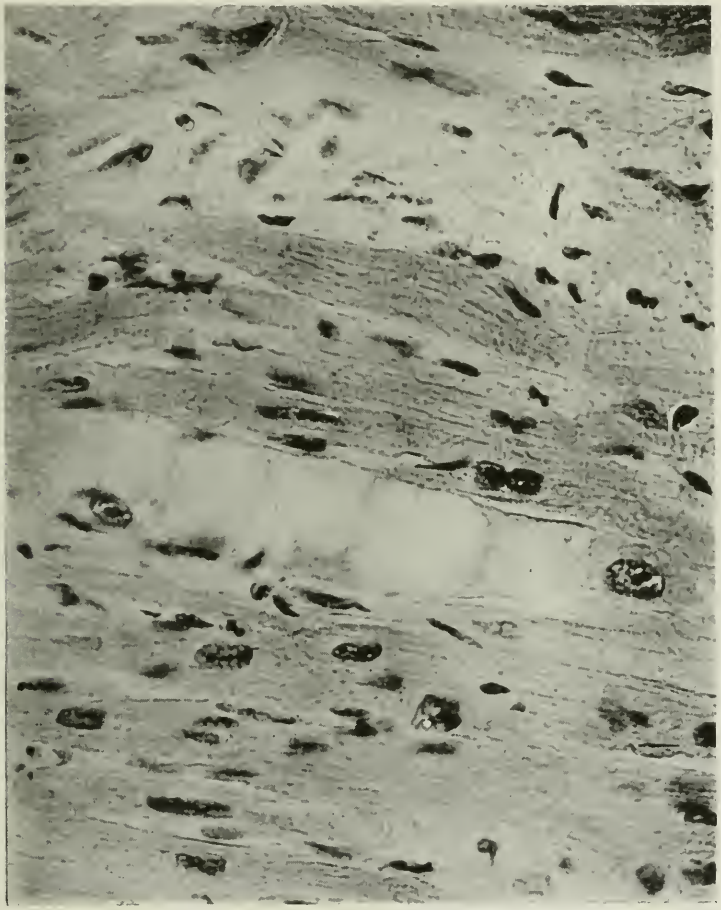

FIG. 2.—Myocardium from Case XI. Marked hyaline necrosis with beginning reparative reaction.

and staining power (eosin) and increased refraction of portions or all of the fibers. The nuclei may show little change in the early cases, but are usually contracted, deformed and more or less

pyknotic. In the more severe or prolonged cases the picture of a hyaline, waxy or typical Zenker's necrosis is presented. The fibers or affected portions of such are swollen, waxy, yellowish or clear, distorted, fragmented, containing large irregular vacuoles,

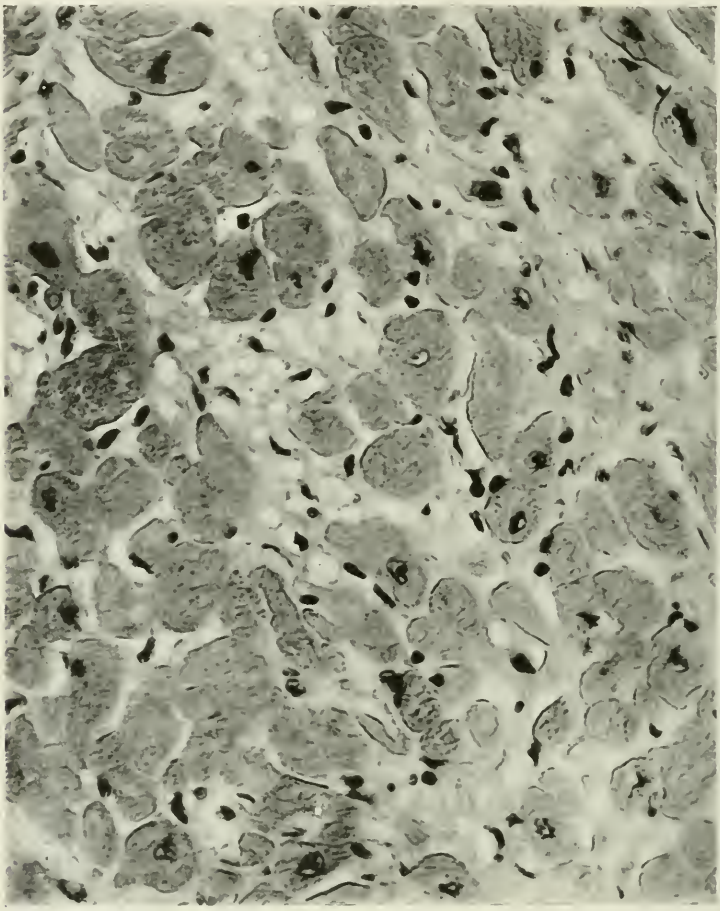

Fig. 3.—Myocardium from same case as preceding. Advanced hyaline degeneration, interstitial edema and beginning fibroblastic proliferation.

or in longitudinal section often partly frayed out, or divided into roundish hyaline segments, with complete loss of nuclei in the affected portions. Living portions of muscle alternate with necrotic

portions. Many of the hyaline dead muscle portions have a high refractive index exceeding that of amyloid. The hyaline degeneration may vary from slight, barely recognizable changes to the picture of complete necrosis.

FIG. 4.—Myocardium from Case III. Advanced hyaline degeneration and necrosis. Interstitial edema, infiltration and beginning fibroblastic proliferation.

The hyaline change may be the only parenchymatous lesion present, but it may be associated with fatty degenerative infiltration, or with cloudy swelling, or with both of these changes.

Marked fatty change was found in only two of our cases. It occurs especially toward the endocardium of the left ventricle and often involves the papillary muscles especially, giving the picture of a tiger-heart microscopically, but which is often not recognized in

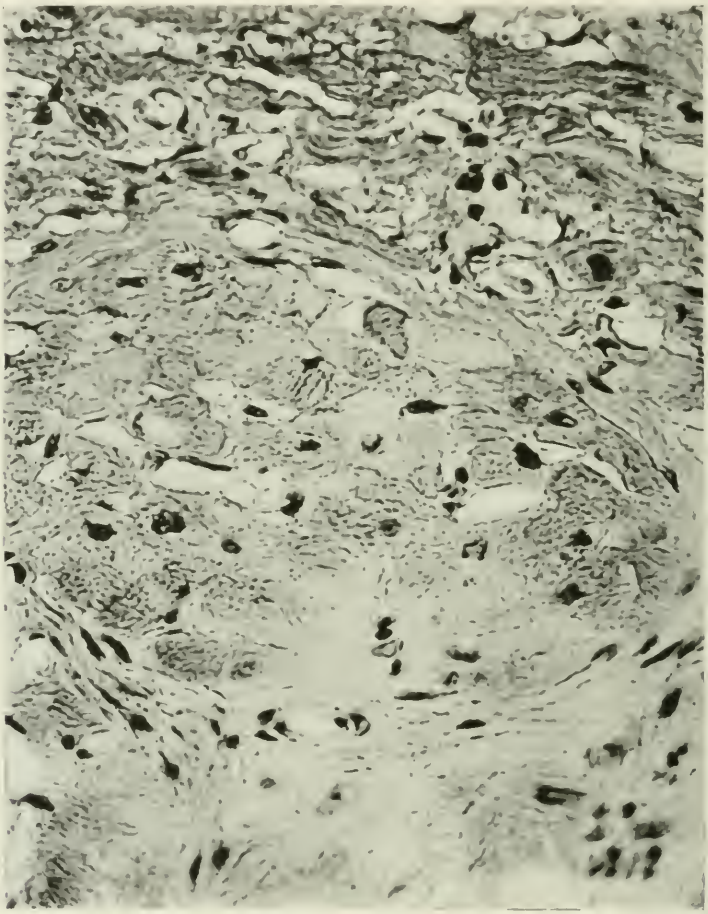

FIG. 5.—Portion of bundle of His from preceding case, showing edema and hydropic vacuolation. Neighboring myocardium shows more marked changes.

the gross because of the associated hyaline change. In our cases fatty degenerative infiltration (so-called fatty degeneration) is certainly not the essential or most frequent lesion. Its association

with hyaline degeneration may be purely secondary to associated nutritive conditions (anemia, asphyxia, etc.).

Likewise cloudy swelling is only an associated change, much less frequent than fatty change. In 1 case only of our series did

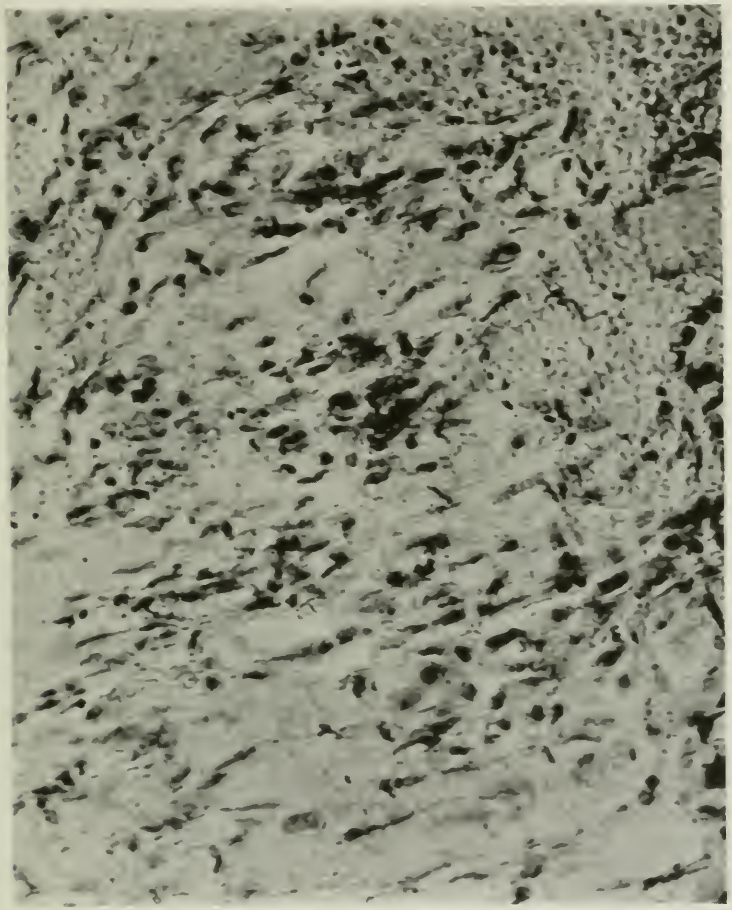

FIG. 6.—Area of muscle regeneration from myocardium of Case III. New fibers growing into area of advanced hyaline necrosis.

it occur extensively in the myocardium, and its association is probably due to nutritional factors.

From the histologic study of these 16 cases we conclude that

hyaline change of the heart-muscle is the essential lesion produced by diphtheria toxin in the heart-muscle. The same thing is probably true of the striped muscles affected by it (diphtheritc paralysis).

Congestion of the coronary vessels and capillaries, small hemorrhages and edema of the interstitial tissues are associated with the parenchymatous lesion.

In the delayed cases, but even as early as the third to the sixth day, lymphocytes and occasional polynuclears and eosinophiles may collect about the small vessels in the stroma of the damaged portions of muscle. No marked collection of eosinophiles was seen in our series. As the interstitial edema increases the appearances of Zenker's necrosis with vacuolation, or of simple hydropic degeneration alone appears. The muscle fibers become fragmented or frayed, partly liquefied and absorbed. Plasma cells and fibroblasts appear in the stroma; the picture of a well-developed myocarditis results. This is apparently wholly reparative in nature. In the older cases regeneration of the heart-muscle occurs to some degree. In Case I (fourteen days) it was well marked; in Case XI (three weeks) the interstitial changes were very pronounced, but the muscle regeneration showed a less advanced stage. A detailed study of these regenerative changes will be given in the complete paper. There is no reason to doubt that diphtheria lesions in the heart may heal completely, leaving more or less fibrosis behind. It is also possible that in the less severely damaged hearts the muscle may be restored to normal or regenerated without fibrosis. Inasmuch as there is a definite association between the two conditions, myocardial degeneration and striped-muscle degeneration, any case of recovery from diphtheria showing post-diphtheritic paralysis of any voluntary muscle is likely to have a more or less damaged myocardium, and in accordance with the severity of the latter damage lies the possibility of cardiac fibrosis and impairment of heart function later in life.

In two cases in which the bundle of His was especially studied, and in a third one in which it was noted, the fibers of the bundle showed the same changes as those of the myocardium in general, but with more marked edema and hydropic vacuolation.

In conclusion, the essential lesion of the diphtheria heart is a toxic parenchymatous hyaline degeneration or necrosis, associated frequently with fatty degenerative infiltration and less frequently with cloudy swelling. The latter two lesions are most probably due to accompanying nutritional conditions. Following the lesion there is (if the patient survives) a reparative inflammatory process (myocarditis) accompanied by muscle regeneration. Either a complete regeneration or a fibrosis may result. The toxin of diphtheria may damage the conducting mechanisms as well as the contractile.

The conflicting pathologic descriptions given in the literature can be unified and the diphtheria heart given a definite entity of an *acute parenchymatous degeneration followed by a reparative inflammation (myocarditis)*. The histologic picture in any given case will depend upon the duration and stage of the infection, upon the degree of toxic injury, the associated nutritional conditions, and the appearance of reparative and regenerative processes.

Note.—The complete and amplified paper will appear, with complete bibliography and illustrations, in the *Journal of Infectious Diseases*.

DISCUSSION

Prof. Wenckebach, Vienna: In the study of muscle degeneration Wiesel considers that the regeneration of fibers is very important and prominent in bloodvessels. He found that there was an enormous amount of muscle regeneration in arteries as well as veins after infectious diseases. In this question of regeneration of striped muscle it is extremely interesting to hear that the first stage of regeneration is comparable to that of smooth muscle. Large masses of smooth muscle may be regenerated in the vessel wall, but there is a difference in the structure of the regenerated portions and the original muscle structure. The whole mass of the regenerated portion appears like a foreign body surrounded by the rest of the smooth muscle tissue; the difference is that there is not the same arrangement of the cells as formerly, the original muscle being arranged in longitudinal and circular layers; but the new muscle formation certainly is active and may serve very well to repair the damage done during the period of infectious disease.

Dr. Bunting, Madison, Wis.: I would like to ask whether there was any evidence of regeneration in children.

Dr. Henry A. Christian, Boston: In regard to the coarser granules seen in two of the slides, I would like to ask Dr. Warthin if these are artefacts.

Dr. A. S. Warthin (closing): All my cases of myocardial degeneration were in young adults eighteen to twenty years old. In regard to the black granules, they are mercuric chloride pigment which was not entirely washed out of the preparation.

STRUCTURAL AND FUNCTIONAL INVOLVEMENT OF THE HEART FOLLOWING ACUTE RESPIRATORY AND OTHER ACUTE INFECTIONS

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AND

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CHICAGO.

Second Paper*

Three years ago, before the 1920 meeting of this Association, one of us (W. W. H.) presented 6 cases of involvement of the auricle and conduction pathways of the heart following influenza.[1] In this report it was stated that epidemic influenza causes damage to the cardiac mechanism which may be demonstrated clinically and electrocardiographically, and that this type of infection singles out, to a degree exclusively, the auricle and conduction pathways. The results of these infections were shown to be chronic cases of cardiac involvement showing arhythmia and involvement of the auricle, persisting and causing partial invalidism long after the subsidence of the acute infection, lasting from twelve to seventeen months and longer. It occurred to us that it might be desirable to reconsider these 6 cases at this time to determine, if possible, the end-results of these acute influenzal infections as to the permanency or lack of permanency of such heart involvement. We have attempted to do this and shall make the first part of this report a brief summary of these cases, with the addition of 2 cases which were observed at that time but were not reported.

* From the Cardiographic Laboratory, Michael Reese Hospital.

The second part will consist of an analysis of 8 additional cases of involvement of the heart following acute respiratory and other acute infections observed during the past nine months, for the purpose of throwing additional light on this type of cardiac involvement, and if possible to broaden and crystallize our views on this subject.

Since our original article one or two noteworthy contributions to this subject have appeared. Paul White,[2] in a general discussion of the heart in infectious disease, considers the effects of influenzal infections to be transient, and speaks of them as temporary poisoning. He believes that many symptoms, such as dyspnea, palpitation and precordial pain, are more likely evidence of effort syndrome or irritable heart than of actual structural cardiac involvement. Likewise, Hamilton and Labey,[3] in an attempt to differentiate hyperthyroidism and heart disease from neurasthenic states, feel that such complaints as breathlessness, tachycardia, heart pain, vasomotor disturbances, etc., are all common to neurasthenia, heart disease and hyperthyroidism. Breathlessness, tachycardia, cyanosis and heart pain do not alone justify the diagnosis of heart disease, as they are found in a variety of conditions, convalescence, fear, fatigue, etc., when the heart is perfectly sound. They emphasize also that neurasthenic states may and frequently do complicate other organic disorders, and that the acute heart disease patient may be disabled by neurasthenic symptoms complicating but in no sense directly due to pathological conditions of the heart. Romberg,[4] in discussing the cardiac findings following influenza, states that acute myocarditis should not be attributed to this condition, and quotes Fahr, who found myocarditis only once among 246 influenza postmortems, although 30 of these cases showed a marked dilatation of the heart. Romberg believes that epidemic influenza produces a functional involvement of the heart muscle, the result of toxic influences, while later certain cardiac symptoms appear, the result of widespread involvement of the entire organism from the infection. He has observed during the epidemic striking symptoms of arhythmia, extrasystoles, conduction disturbances, dilatation and muscular mitral insufficiency; during convalescence, evidences of heart weakness, angina-

like attacks, here and there arhythmias or marked bradycardias. The duration of the heart involvement he found ranged from a few days or weeks to several years, and mentions 1 patient, a man, obese, a heavy wine drinker, nervous, who experienced shortly after an influenzal attack his first heart involvement and died within eighteen months of heart-muscle insufficiency. His markedly dilated heart showed even with the most careful microscopic study no other demonstrable pathologic changes, no evidence of coronary sclerosis, myocarditis, fatty degeneration of the muscle fibers or other changes in the musculature.

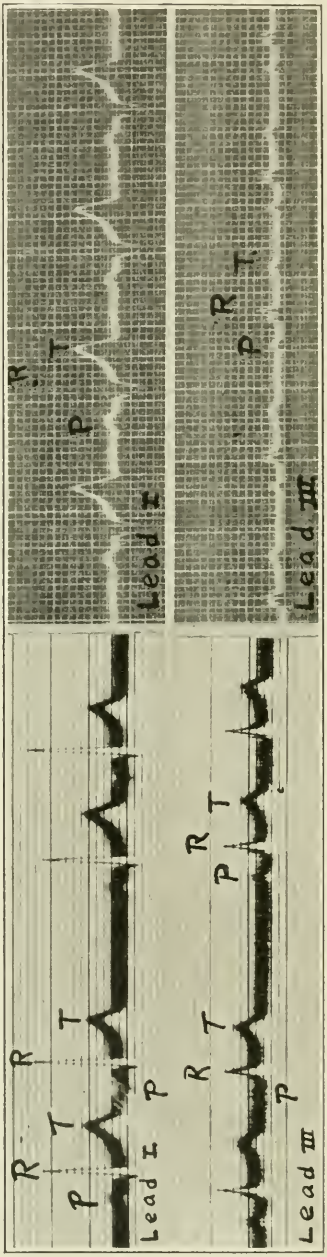
TABLE I.—CASES REPORTED 1920–1921. SUBSEQUENT REPORT.

Case.	Diagnosis (1920).	Present status (1923).
1 S. R.	Postinfluenzal auricular myocarditis.† Pulsus bigeminus. Auricular extrasystoles.	Marked improvement. Only occasionally shortness of breath. Complete disappearance of extrasystoles and bigeminus.
2 Dr. S.	Postinfluenzal myocardial insufficiency.	Not heard from.
3 C. H. W.	Postinfluenzal right ventricular extrasystoles. Ectopic auricular contractions.	No complaints. Occasional extrasystole. EKG shows inverted P_2 and right ventricular extrasystoles.
4 Dr. B.	Acute streptococcus myocarditis,† with auricular extrasystoles and partial A-V block.	Entirely recovered. "No heart lesion that can be detected."
5 Miss E. S.	Acute streptococcus myocarditis,† with partial 3–2 A-V block.	Not heard from.
6 Miss H. N.	Chronic postinfluenzal myocarditis,† with auricular extrasystoles.	Only slight improvement. Frequent attacks of "grippe." Tires easily. Auricular and ventricular extrasystoles.
7 J. M.	Acute postinfectious (streptococcus) myocarditis.† Acute, complete A-V and right bundle branch block.	Entirely recovered. EKG normal.
8 J.C.	Post-infectious (streptococcus, diphtheria) myocarditis,† and nephritis.	Entirely recovered. EKG normal.

† Not based on histological examination.

Of the 8 cases reported in 1920, we have been able to trace 6.

CASE I.—A teamster, aged twenty-five years, who, following a severe attack of influenza in April, 1919, was completely incapacitated from his occupation, was listed in our earlier report as a postinfluenza auricular myocarditis, pulsus bigeminus and auricular extrasystoles. In April, 1920, a year after his influenza infection, this patient was able to take care of a small newsstand, to which occupation he was obliged to change because of his inability to work as a teamster. Examination in April, 1923, four years after his influenza, shows him markedly improved and apparently free from symptoms except occasional shortness of breath on severe effort. Evidences of dilatation of the heart have entirely disappeared, his heart borders being



Series I. Series VI.

Fig. 1.—Case No. I. S. R. (teamster), post-influenzal auricular myocarditis. Series I, pulsus bigeminus, auricular extrasystoles (taken in 1920 during acute infection). Series VI, normal cardiac mechanism, showing absence of extrasystoles and bigeminus (taken April, 1923).

within normal limits. There is no evidence of auricular extrasystoles or bigeminal pulse, which three years ago were brought out particularly on exercise. Figs. 1 and 1 A. show a comparison of his electrocardiographic curves in 1920 and 1923, showing the complete disappearance of the auricular involvement.

This case then should be put down as a complete recovery from a rather widespread involvement of the auricle following influenza within a four-year period.

Case II.—Physician from the South, we have been unable to locate.

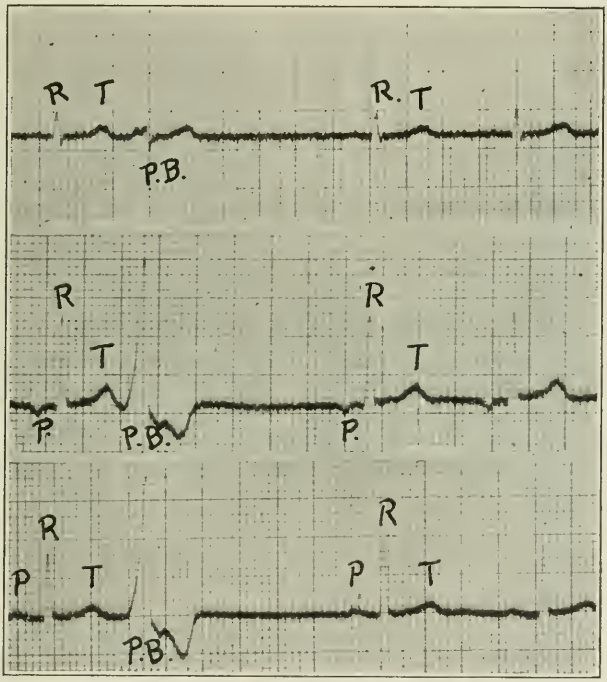


Fig. 2.—Case No. III. C. H. W. (merchant), right ventricular extrasystoles, inversion of P_2 probably indicative of abnormality in the origin and path of the excitation wave in the auricle, inversion of P_3 present in curves three years ago not present now.

Case III.—Merchant, aged thirty years, with influenza, in September, 1918, and recurrence in November, 1918, was diagnosed as a postinfluenzal auricular and ventricular involvement with right ventricular extrasystoles and ectopic auricular contractions. Examination in February, 1923, four

and a half years after his influenza, shows no symptoms or complaints of any description; no dyspnea; an occasional extrasystole still present. Fig. 2. shows his present electrocardiographic curves.

Case IV.—Physician, aged twenty-eight years, who was diagnosed in 1920 as acute streptococcic myocarditis involving particularly the auricle and conduction pathways, reports by letter, March 25, 1923: "I have never felt better in my life. Since leaving the hospital I have refereed football games, have danced and taken more exercise than I have in a number of years, all without discomfort. I have no heart lesion that can be detected. My blood-pressure is 135/80. I am still overweight, but I have lost twenty-five pounds since I have been here. I have been able to take out life insurance, being rated up a little on account of my weight. Otherwise I am O. K."

Case V.—A pupil nurse. This patient we were unable to locate.

Case VI.—Stenographer, aged twenty-eight years, who believed her heart trouble followed the "flu" in October, 1918, and who was diagnosed as chronic postinfluenza myocarditis with localization in the auricle resulting in auricular extrasystoles, has not made as satisfactory a recovery as the others. She has had repeated attacks of grippe, becomes exhausted easily, has had transitory attacks of vertigo with numbness of extremities and occasional precordial soreness. Examination at the present time shows a rapid pulse, irregular in rhythm and force; right heart border 3.5 cm., left 10.5 cm. from the midsternal line; slight unclearness of the first tone of the apex which becomes more noticeable on sitting up; 10 to 12 extrasystoles per minute. Fig. 3 shows the original curve and the electrocardiogram at present, showing in addition to the original auricular involvement, extrasystoles arising also from the ventricle. One must conclude that this patient still shows evidence of both auricular and ventricular involvement and should continue under observation to determine, if possible, the final outcome of the heart findings.

Case VII.—This patient, a boy, aged thirteen years, was not included in the original 6 cases but was published a few months later in the Chicago Number of the *Medical Clinics of North America*.[5]

Following an acute follicular tonsillitis, from which pure cultures of hemolytic streptococcus were isolated, this boy, developed on the sixth or seventh night of his illness, shortly after midnight, a sudden and complete auriculoventricular heart-block with a radial pulse of 28 beats per minute (Fig. 4). At the time this boy was diagnosed as an acute postinfluenza (streptococcus) myocarditis, involving particularly the bundle of His and its branches and resulting in transitory complete auriculoventricular dis-

sociation and right bundle-branch block. Two weeks after the onset, however, electrocardiogram showed a practically normal cardiac mechanism, and a week later he left the hospital apparently entirely recovered (Fig. 5). At the present time he is entirely recovered, is free from complaints of any description and is attending school preparing himself for a professional career. Physical and electrocardiographic examination are negative (Fig. 5A).

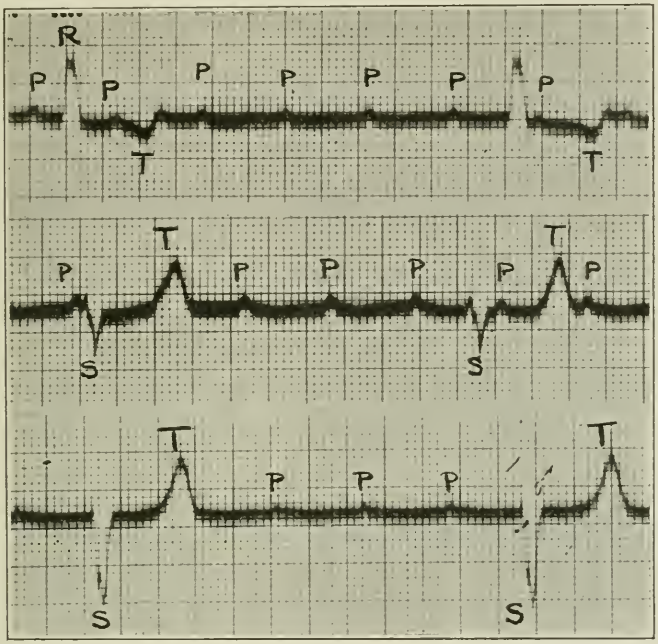


Fig. 3.—Case No. VII. J. M., school boy, aged thirteen years, acute infectious (streptococcus) myocarditis with complete A–V and right bundle branch block. Leads I, II, III taken October 27, 1920, on entering hospital. First published Medical Clinics North America, July, 1921.

Case VIII.—The eighth case, which occurred at about the same time as the others, but reported now for the first time, concerns itself with a young man, aged thirty years, a salesman, who, following an acute streptococcus and diphtheritic sore throat early in 1921, developed weakness, dyspnea on exertion, bradycardia, palpitation and pain. Examination showed a moderate dilatation of the heart, the left heart border being $1\frac{1}{2}$ cm. outside of the left nipple. The other findings were negative except those traceable to a subacute glomerular nephritis, *i. e.*, albumin, granular casts and a blood-pressure of 140/90, slight diminution of his thalein output and increase in the non-protein nitrogen of the blood. Examination on

March 19, 1923, shows a slight increase in the degree of left ventricular preponderance as compared with his findings two years before.

Summarizing the results of these 8 cases, 5 patients present no complaints, particularly no cardiac complaints, and have apparently entirely recovered from the effects of their influenzal involvement. One patient still shows evidence of auricular and ventricular disease and 2 patients cannot be traced. One must conclude, therefore, with White, Romberg and others, at least so far as this small series is concerned, that the effects of influenza are transitory in character, that although widespread involvement of the heart may be demonstrated at the time of or shortly following the acute infection, within a four-year period these effects have completely disappeared. From the findings of these cases it is extremely difficult, however, to conclude finally as to the exact nature of the involvement following influenza in terms of pathological anatomy and pathological physiology. One is not quite satisfied with the statement of an acute poisoning, but without experimental or histologic findings it is impossible to say whether the effects observed might be due to cloudy swelling, edema, acute myocarditis, acute neuritis of the vagus or other pathologic involvement. In this connection, White speaks of a transient heart-block occurring in rheumatic fever in hearts which do not show signs of pathologic changes or pericarditis. He concludes that the occasional finding of acute heart-block should make one feel that any person who has suffered from rheumatic fever is not likely to have a perfectly normal heart even though it appears normal to auscultation and percussion. Cowan, Fleming and Kennedy,[6] found in a girl, aged ten years, dying of diphtheria, with complete heart-block, on sections of the auriculoventricular node and bundle, an acute inflammatory process, with separation and diffuse interstitial inflammation of the muscle fibers. In a male, aged twenty-six years, with heart failure following a cold and death from cerebral embolism, section of the heart showed marked congestion of the auriculoventricular node, with small foci of round-cells in the bundle and early interstitial myocarditis.

Magnus Alsleben[7] found in 4 cases of heart-block studied micro-

scopically that a transient partial heart-block is of frequent occurrence during the course and convalescence of acute infectious disease, and concludes that there is probably no lesion of the bundle itself, the block being vagal in origin.

Gerhardt[8] reports the case of a man dying from typhoid fever, who previously had a transitory heart-block following rheumatism. Examination showed a definite lesion of the bundle, consisting chiefly of cellular infiltration chiefly in the region of the vessels.

Allen[9] believes and quotes Lewis in support that all transitory blocks are on the basis of organic lesions of the bundle rather than on vagus effects, and concludes that such evidence of involvement of the bundle by partial or transitory block is certain evidence of myocardial change.

As we stated in the 1920 report, we have had no opportunity for microscopic study of hearts following influenza and showing clinical and electrocardiographic evidence of involvement of the conduction pathways, so that direct proof of this point cannot be offered in this series of cases. However, from our experience and a study of the literature we incline to the view that partial or complete block is due to organic changes in the bundle rather than to vagal influences, although conceivably, both might be present. The fact that these changes may be transitory does not itself speak against this view.

Also our experience that the majority of these cases cleared up within a three- or four-year period does not speak against this conclusion. Either the scarring of the bundle, the theoretical result of such involvement, could be of such degree which would not affect the conduction pathways, or the cloudy swelling, edema, hemorrhage, cellular infiltration and acute interstitial inflammation which formed the structural basis of the detected temporary functional defect might be entirely recovered from. Whether or not involvement at one time predisposes to a repetition at a later date we have no experience which is relative.

New Cases in 1923. The 8 new cases observed during the past nine months we believe show evidence of both structural and functional involvement of the heart, the relative degree of each factor varying in the individual case. We have therefore divided

these 8 new cases into two groups of 4 each, the first with predominant structural involvement, in which definite and unmistakable evidence of organic heart involvement can be demonstrated with a lesser degree of functional symptoms; the second, in which the functional involvement predominates while definite structural disease is either slight or questionable. The majority of these cases have followed acute influenzal infections or some complication thereof.

TABLE II.—CASES SHOWING PREDOMINANCE OF STRUCTURAL HEART INVOLVEMENT.

Case.	Etiological diagnosis.	Structural diagnosis.	Functional diagnosis.	EKG diagnosis.	B.M.R.
No. 9 Mrs. W.	Influenza; pneumonia	Subacute† myocarditis	Early heart failure	Partial A-V block	7.2% plus.
No. 10 Mrs. L.	Influenza; pneumonia; acute arthritis; empyema. * Measles; diphtheria; epidemic influenza, 1919	Subacute† myocarditis and endocarditis; mitral stenosis, aortic insufficiency	Moderately advanced heart failure	Partial A-V block; right bundle branch block	20.0% plus.
No. 11 Mrs. G.	Influenza; pneumonia * Diphtheria 7; pneumonia 1918	Chronic myocarditis† and endocarditis; mitral stenosis and regurgitation	Moderately advanced.	Sinus rhythm	20.1% minus.
No. 12 Mr. P.	Peritonsillar abscess (streptococcus) * Pneumonia 9 years ago	Subacute endocarditis; mitral insufficiency; subacute glomerular nephritis	Moderately advanced heart failure	Sinus rhythm	12.8% plus.

* Acute infections above, previous infectious diseases below the line.
† Not confirmed by histological examination.

Predominant Structural Involvement. The first patient of the "structural group" (Case IX) is a woman, aged thirty years, who developed in October, 1922, a diffuse bronchopneumonia following influenza, during the course of which she showed a rapid, irregular pulse which proved to be a partial auriculoventricular block (Fig. 6). The discharge diagnosis was postinfluenzal bronchopneumonia, postinfluenzal subacute myocarditis with partial auriculoventricular heart-block. The heart was moderately enlarged to the left; the blood-pressure was 102/78.

This patient is still under observation. Her heart is now rapid but regular and enlarged to the left. She still complains of marked dyspnea on only slight walking, precordial pain, has a very limited cardiac reserve; becomes quickly exhausted on slight effort, and is pale, gray looking and cyanotic. She had had no acute infectious diseases prior to her pneumonia. She is nervous, depressed, worries a great deal regarding her condition and runs an occasional slight afternoon temperature. We consider the partial auriculoventricular block, dyspnea, cyanosis and enlargement of the heart

and easy exhaustion due to structural disease; the other symptoms are functional.

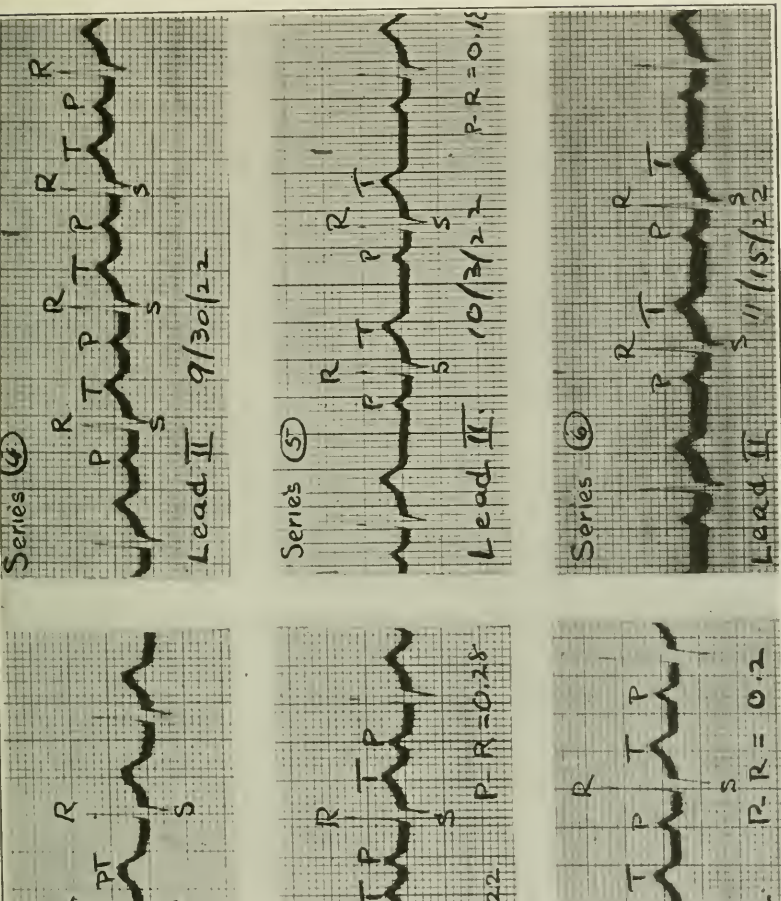


FIG. 4.—Case No. IX. Mrs. S. W., aged thirty years, housewife, influenzal bronchopneumonia, postinfectious subacute myocarditis with partial A-V heart block. Series of six electrocardiograms (Lead II) taken at varying intervals during course of infection (six months), from first series taken at the height of infection to last showing restoration of normal cardiac mechanism.

The second patient (Case X), a young married woman, aged twenty-six years, developed six weeks prior to her admission an acute infectious arthritis and three weeks later an acute pleuritis with bronchopneumonia and empyema. She had measles, mumps and diphtheria as a child and influenza in 1919. The completed diagnosis was acute infectious arthritis, influenzal bronchopneumonia and empyema, postinfectious subacute endocarditis and myocarditis, with aortic insufficiency and mitral stenosis, partial auriculoventricular and bundle-branch block (Fig. 7). She had some evidence of thyroid involvement, her basal metabolism rate being 20 per cent plus a blood-pressure of 142/80 and pulse 112 (Fig. 8).

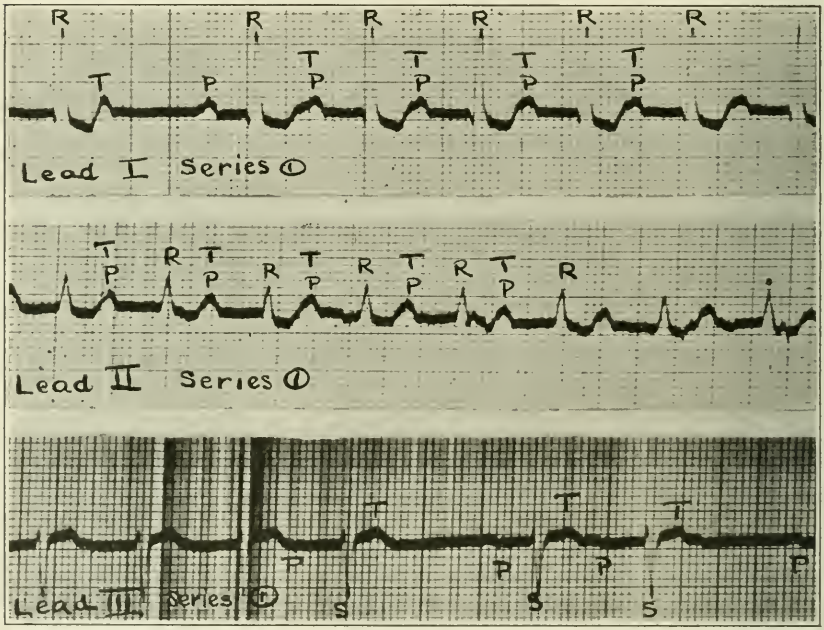


FIG. 5.—Case No. X. Mrs. E. L., aged twenty-six years, housewife, combined rheumatic and postinfluenzal heart disease, influenzal bronchopneumonia with empyema; postinfectious subacute myocarditis with partial A–V heart block, and right bundle branch block; subacute mitral and aortic endocarditis with mitral stenosis and aortic insufficiency. Tracing made September 13, 1922 (Series I), two months after onset of rheumatic infection and one month after onset of acute lung infection.

She apparently has completely recovered and is able to be out of bed and perform her household duties, with no evidence at the present time of heart failure. This patient was extremely ill for many weeks; lost between 40 and 50 pounds in weight; was at times deeply cyanotic with orthopnea, with enlarged tender liver, etc.; at all times frightened, depressed, appre-

hensive, complaining of insomnia, anorexia, etc. Her breathing and pulse were at times extremely rapid. She needed many months to regain her equilibrium, cardiac reserve and ability to walk about. We feel the mitral and aortic disease, conduction-path involvement, dyspnea, heart dilatation and cyanosis are due to structural disease; many of the other findings either functional (effort syndrome?) or related to the thyroid involvement.

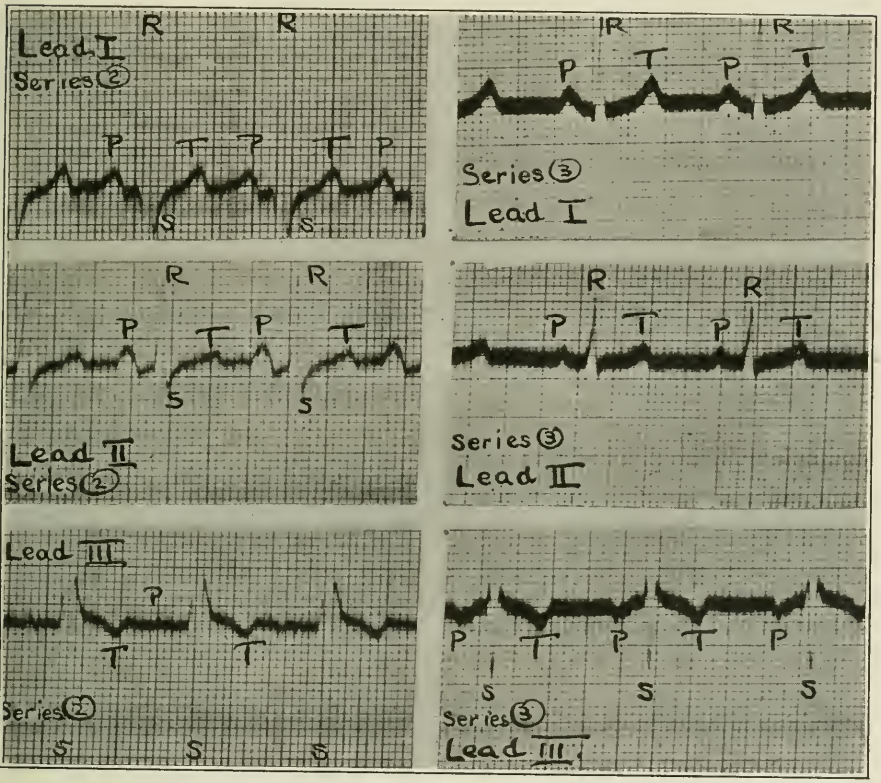


FIG. 6.—Case No. X. Mrs. E. L. Series (II) and (III), postinfectious A–V and bundle branch block; Series (II) made November 18, 1922, two months after Series (I); Series (III) made February 27, 1923; five months after Series (I). Both show disappearance of A–V and intraventricular block and gradual return to normal cardiac mechanism.

The third patient (Case XI), a married woman, aged thirty-five years, has early, slight heart-muscle failure with mitral stenosis and regurgitation, apparently the result of epidemic influenza and pneumonia in 1918. Her blood-pressure in 120/80. When first seen she had limited response to effort, edema of ankles, cyanosis and decreased urinary output. On rest in bed and moderate amounts of digitalis she apparently has completely

recovered. Her findings are all structural in origin except the attacks of simple tachycardia, anxiety, depression, etc., which we interpret as being of psychogenic character.

The fourth patient (Case XII), a man, aged thirty-seven years, who, following a peritonsillar abscess in which hemolytic streptococcus was found, developed swelling of the feet and legs, decreased urinary output, pallor, dyspnea, rapid pulse and weakness. Blood-pressure varied from 140/100 to 157/92. His urine showed occasional blood, a large number of casts and considerable albumin. He had had pneumonia nine years ago. His right heart border was 3 cm. and the left 9 cm. from the midsternal line, with a soft presystolic and systolic murmur at the apex. He was diagnosed postinfectious heart disease, subacute mitral endocarditis with mitral insufficiency and stenosis and moderately advanced heart failure. His pulse at all times has been extremely rapid.

The electrocardiogram showed an inversion of the T-wave in the first lead. He is still under observation and is dyspneic on effort and is pale. The majority of his findings we believe are on an organic basis.

Summary. These 4 cases we believe show that, as a result of these acute infections, various portions of the heart, endocardium and myocardium or both are involved, and that although marked recovery has occurred during these early months, at least in 2 of them evidence of heart failure still exists. We conclude that acute influenzal infections cause structural damage to the heart even as the older, better recognized infections, acute rheumatic fever, diphtheria, etc. We believe that following these acute respiratory infections the development of valve murmurs (particularly diastolic), cyanosis, dyspnea, orthopnea, diminished urinary output, enlarged tender liver, auriculoventricular or bundle-branch block, enlargement of the heart to percussion are clear evidences of organic disease. The fact that under adequate treatment most or all of these findings are relieved does not, we believe, speak against this view. The rather constant association of nervousness, depression, anxiety, insomnia, anorexia, occasional tremor, tachycardia, breathlessness, precordial pain and easy fatigue are functional or thyroid in origin. Of particular interest and emphasized here for the first time, so far as we know, is the association of these two groups of findings in these patients suffering from the results of these acute respiratory infections.

Predominant Functional Involvement. The following 4 cases show evidences of marked functional and questionable structural involvement of the heart:

TABLE III.—CASES SHOWING PREDOMINANCE OF FUNCTIONAL HEART INVOLVEMENT.

Case.	Etiological diagnosis.	Structural diagnosis.	Functional diagnosis.	EKG diagnosis.	B.M.R.	Neurological diagnosis.
No. 13 Mrs. S.	Influenza (epidemic 1918) * Diphtheria 9; chorea 13. Diarrhea with fever 3 and one and a half years ago	Subacute myocarditis†	Early heart failure (?) effort syndrome	Low voltage; inversion and notching R3	21.7% minus	Anxiety state.
No. 14 Mrs. F.	Puerperal infection; Cesarean section. * Diphtheria 5; typhoid 15. Epidemic influenza 1918; acute inflammatory rheumatism 1918	Subacute† myocarditis	Early heart failure (?) effort syndrome	Low voltage; inversion and notching R3	14.9% plus	Major hysteria.
No. 15 Mrs. R.	Epidemic influenza (1918)	.....	Effort syndrome	Paroxysmal tachycardia	1.4% minus	Anxiety state.
No. 16 Mrs. B.	Epidemic influenza (1918) * Scarlet fever 4; typhoid 11	Subacute† myocarditis Subacute thyroiditis	Thyrotoxic heart	Low voltage; inversion and notching R3	17.1% plus	Hyperthyroidism.

* Acute infections above, previous infectious diseases below the line.
† Not controlled by histological examination. Autopsy findings in similar cases show only dilatation.

The first patient (Case XIII), a married woman, aged thirty-five years, complains of occasional palpitation of the heart, attacks of pain under the left breast of three years' duration, the first attack occurring following acute diarrhea and fever three years ago. She had diphtheria at nine and chorea at thirteen. Examination is essentially negative. Blood-pressure is 112/60 and basal metabolism 21.7 per cent below normal. She was diagnosed as postinfectious myocarditis (?) and anxiety state. The electrocardiogram showed an extremely low voltage in the third lead with inversion of the initial ventricular complexes, a frequent finding in these postinfectious functional cases (Fig. 9). Under preliminary rest in bed, later graded exercise, reassurance regarding her condition, alternating thyroid and bromide medication, she has made satisfactory progress.

The second patient (Case XIV), a married woman, aged twenty-nine years, complained of dyspnea, extreme nervousness and continuous temperature since the birth of her third baby, five months previous. She had diphtheria at five and typhoid at fifteen, epidemic influenza and pneumonia in 1918 and acute infectious arthritis in 1918. She is a large, obese, pale and unhealthy looking woman. Her basal metabolic rate is 14.9 per cent above normal. The electrocardiogram is negative except for the same low voltage and inversion of the Q R S group, as in the previous case. She was diagnosed as postpuerperal myocarditis, major hysteria and subacute hyperthyroidism. She is somewhat improved at the present time.

The third patient (Case XV), a young married woman, aged thirty-five years, suffered severe, sudden, acute attacks of tachycardia which we believe were true paroxysmal tachycardia, the first attack occurring four years ago following epidemic influenza. She has had no other acute infectious diseases. Examination is essentially negative except that she is extremely thin and poorly nourished. The electrocardiogram is negative except for low voltage in the third lead. Although she is improved, any severe emotional display is apt to be followed by an abrupt onset of her tachycardia.

The fourth patient (Case XVI), a married woman, aged thirty years, believes she has not been well since influenza in 1918 and again a grippe attack in September, 1922. She complained of an extremely rapid pulse with failure to gain weight. She has no dyspnea. Examination shows an enlargement of the left thyroid lobe and a metabolic rate of 17.1 per cent +, pulse 188 and blood-pressure 144/88. She was diagnosed as postinfluenzal subacute myocarditis and thyroiditis with hyperthyroidism. Under complete rest in bed, bromides and occasional small amounts of digitalis she has made a satisfactory gain. She had scarlet fever at four and typhoid at eleven.

These 4 cases may be discussed together. We conclude that, in view of the findings of palpitation, precordial pain, periodic attacks of nervousness, exacerbation of cardiac symptoms following emotional excitement, persistent tachycardia and breathlessness, presence of depression and anxiety states, this type of case following epidemic influenza is largely functional in origin of the group variously called irritable heart, effort syndrome, neurocirculatory asthenia. The fact, however, that they failed to recover entirely under treatment directed to such functional disorder, but have recovered following prolonged bed rest and digitalis, in addition to adequate psychologic management, justifies the conclusion that a minor portion of their complaints are of structural origin.

Summarizing the significant facts in these two groups of cases we find the following: They all show the development of their cardiac symptom following acute respiratory infections (influenza). The significance and interpretation of these cardiac symptoms are of two types, one structural and the other functional, the relative degree of each varying in the individual case, in 4 being predominantly structural and in 4 functional. The majority of these cases have secured either complete recovery or marked improve-

ment, the result being attained by a combination of treatment directed toward both structural and functional disease. We believe, therefore, that in the evaluation of this type of cardiac trouble following epidemic influenza, it is of service to consider in each case the possibility of such dual disease, as we have found with such consideration the effects of treatment are markedly enhanced. In other words, instead of attempting definitely to separate organic from non-organic findings, this series of cases presents evidence representing a dual involvement. We desire to point out this possibility in each instance of postinfluenzal cardiac disease.

Considering these 16 cases as a whole, our first group of 8 cases of three years ago and the present series of 8 cases observed this past year, we reach the following conclusions: Acute respiratory infections (influenza) may and frequently do produce cardiac symptoms. These symptoms are often caused by both structural and functional involvement of the heart. Structural involvement is recognized by delayed conduction time, partial, complete or bundle-branch block, enlargement (dilatation) of the heart, endocardial murmurs and signs of early heart failure. Functional involvement is recognized by palpitation, precordial pain, fatigue, weakness, nervousness, anxiety, depression, cyanosis, dyspnea, pallor, tachycardia. These two groups of symptoms may and frequently do coëxist in the same patient, and it is this coëxistence of structural and functional involvement which we wish to especially emphasize. Structural involvement is often evident first, may be entirely overlooked, is often extremely transitory. Functional involvement appears later, often dominates the clinical picture, usually requires a longer period for relief.

Conclusions. 1. A reconsideration of 8 cases of postinfluenzal cardiac disease first observed and reported in 1920–1921 shows 5 completely recovered, 2 not traceable and 1 unimproved.

2. Eight new cases of cardiac involvement following acute respiratory infection observed during the past nine months present evidence of both structural and functional involvement, half predominant structural, half functional.

3. Diastolic murmurs, enlargement of the heart to the left,

swelling and tenderness of the liver, edema of ankles and diminished urinary output, auriculoventricular and bundle-branch block serve as criteria of structural disease; palpitation, tachycardia, precordial pain, nervousness, depression, anxiety states are suggestive of functional involvement; breathlessness, cyanosis, weakness, exhaustion, fatigue are of indeterminate interpretation and significance.

4. The possibility of coëxistent structural and functional disease should be borne in mind in a survey of any postinfectious heart patient. Treatment directed toward amelioration of both types of symptoms offers not only the most favorable chance of recovery, but may be of differential diagnostic value.

5. Delayed conduction time, partial, complete or bundle-branch block, occurring at the height of an acute respiratory infection may be interpreted as structural heart involvement. The fact that such findings may be based on extremely slight or negative histologic findings and are transitory in character does not of itself speak against this view.

6. It is desired to especially emphasize the coëxistence of structural and functional involvement of the heart (following influenza) in the same patient. Structural involvement is often evident first, may be entirely overlooked and is often extremely transitory. Functional involvement appears later, often dominates the clinical picture and usually requires a longer time for relief.

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DISCUSSION

Dr. E. B. Krumbhaar, Philadelphia: I would like to ask whether there were any preinfluenzal studies made in order to rule out the long arm of coincidence.

Prof. Wenckebach, Vienna: In such cases the diagnosis of myocarditis has not been made. Some of the influenzal cases are those of functional disorder of the heart, delayed conductivity or heart-block. This functional disorder may be set up by toxic agents or perhaps by fatigue. In influenza I have seen cases of delayed conductivity. This was during convalescence, and the man was perfectly well afterward. MacKenzie has stated that there may be a complete dissociation between auricles and ventricles, but not with complete recovery. Such cases may be myocarditis but proof has to be given, and this cannot be obtained until the cases are complete. We know that we can set up a heart-block with digitalis or a prolongation of the auriculoventricular interval, but none of us would admit that digitalis will set up myocarditis.

Dr. Hamburger (closing): In answer to Dr. Krumbhaar, we had no previous experience with these patients, but there was no history of cardiac disturbance before influenza developed. I do not want to say that auriculoventricular block is evidence of structural disease. The cases diagnosed as structural disease were those which showed other symptoms, as large, tender liver, scanty urine, dyspnea and temporary signs of heart failure. Although these cases cleared up, we can conceive of them as true structural involvement. This may be cloudy swelling or edema, tissue change of an acute nature but capable of being restored to normal.

THE VALUE OF THE *X*-RAY IN DIAGNOSIS OF CHRONIC VALVULAR HEART DISEASE

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Most of the application of *x*-ray methods to the study of the heart have been in reference to the frontal plane projection of the organ. The methods originating in Germany through the work of Moritz,[1] Dietlen,[2] Groedel,[3] Levy-Dorn[4] and others, and continued in France, especially by Vaquez and Bordet,[5] and in this country by Bardeen,[6] Betrand Smith,[7] H. W. Smith and Bloedorn,[8] Danzer,[9] and Cohn,[10] consist of either the distant *x*-ray photograph or teleroentgenogram and the use of the orthodiagram. Measurements of various diameters and the area of the cardiac silhouette have been made by various workers mainly in an attempt to establish average normals and range in normal subjects as a basis for the study of departure in disease. In the more recent work there has been a tendency to lay stress particularly on the greatest transverse diameter and the area of the silhouette as of practical value and to bring these measurements into relationship with the height and weight of the individual. The rather extensive tables of Bardeen[6] and Dietlen[2] for all ages and size of body and those of Betrand Smith,[7] H. W. Smith and Bloedorn,[8] Danzer[9] and of Cohn[10] on restricted age groups have served to establish a satisfactory average curve and to show that this increases in relation to body height and weight. With the exception of Betrand Smith, however, the variations from the average are quite wide, necessitating the recognition of considerable apparent normal variations,

so much, indeed, as to lead Smith and Bloedorn to conclude, from a study of 500 subjects in a restricted age group that the results can be applied clinically only with great reserve. Smith and Bloedorn also attempted to correlate their data with the surface body area as determined by Du Bois' tables, but obtained little reduction in average variations. The French workers, particularly Vaquez and Bordet, have extended the general method to include examination in planes other than the frontal, and have developed most extensive and detailed procedures. These methods, with few exceptions, are observational rather than concerned with mensuration.

Our effort has been to determine the influence of certain factors which may enter into the results obtained in so-called normal series and to attempt a study of the results obtained on application of the frontal plane method and certain other procedures in groups of clinical cases.

In regard to the first question, concerned with the limits of variation in normal individuals of the cardiac frontal contour area and transverse diameter, most writers have assumed a variation of at least ±10 per cent from the average curve. This variation is supposed to take care of variations of heart mass above and below the average and errors of technic in the determination. The first data that we wish to present is in regard to variations within the same individual at different examinations. Table I is compiled from twenty determinations made on 17 individuals. There is an average variation of 6 per cent in area and 4 per cent in transverse diameter. Influence of moderate exercise is shown in Table II. The subjects rested fifteen minutes before the first orthodiagraphic examination and then went out for a fifteen-minute walk. There was an average variation of 5.1 per cent in area and 0.7 per cent in transverse diameter. The influence of a meal was similarly determined (Table III), the subjects resting fifteen minutes in the prone position before each determination. This showed an average variation of 5.7 per cent in area and 3.7 per cent in transverse diameter. So far as we know in none of the normal data published has the matter of variation in the same individual, from time to time, nor the influence of activity nor meals been considered. If

TABLE I.—VARIATIONS IN SAME INDIVIDUAL. IN TERMS OF FIRST EXAMINATION. AFTER FIFTEEN MINUTES' REST

Subject.	Frontal percentage area.	Orthodiagram change in trans. diam.	Percentage change in pulse-rate.	Interval.	
1	+6	−9	−2	1 week	Controlled[1]
	+4	−3	+10	2 weeks	
2	+7	−3	+8	1 week	"
3	−2	0	−9	1 week	"
4	−3	0	−13	2 weeks	"
5	−11	+7	+3	3 weeks	"
6	−11	+3	−3	1 week	"
7	−4	+1	0	1 week	"
8	−8.3	−4.2	+7.5	1 week	"
9	+2	−3	.....	5 months	A.R.M.R.
10	−3.2	+4	.....	5 months	M.St.
11	−3	−2	.....	7 weeks	M.R.
12	+12	+2	.....	5 weeks	Normal
13	+13	0	.....	1 month	Normal
	+3.5	+2	.....	3 weeks	
	+17	+9.2	.....	4 months	
14	+6	+1	.....	10 months	Normal.
15	+19	+1	.....	4 months	M.R.(?)
16	+10	+9.1	.....	5 weeks	M.R.
17	0	−5	.....	6 months	M.R.
Average	6	4			

TABLE II.—INFLUENCE OF FIFTEEN MINUTES' WALK

Subject.	Frontal percentage area.	Orthodiagram change in trans. diam.	Percentage change in pulse-rate.
1	+16	0	+20
	+10.5	0	+14.5
2	−1	−2.5	+30
	−4	+4	+11.5
3	−9	−4	+21
4	+10	+4.8	+10
5	+1	−2	+13
	−1	−3.7	+18
6	−1	+2.5	+16
7	+5	0	+30
	+17	+7	+13.5
8	−2	−4	+5
	−4	−1	−6
9	−2	−7	+40
10	+2	−6	+23
11	+3	+5	+13
12	+3	−4	0
	+18	+4.5	+4.5
Average	+5.1	−0.7	+24

[1] By "controlled" is meant that subject rested in prone position for fifteen minutes before each determination.

the possible average variations are added it is evident that unless these matters are controlled or are taken into consideration that a total possible variation above the so-called normal average of 26.8 per cent in area, and 18.4 per cent in transverse diameter may be expected, and if the range of individual variations is taken into account that figures approximating 50 per cent in area and 30 per cent in transverse diameter may conceivably result.

TABLE III.—INFLUENCE OF A MEAL AFTER FIFTEEN MINUTES' REST

Subject.	Frontal percentage area	Orthodiagram change in trans. diam.	Change in pulse-rate in per cent.	R/L ratio	
				Before.	After.
1	+2.0	+6.0	+12	1.80	1.00
2	+8.3	+3.3	+17	1.50	1.00
3	−3.3	+3.0	−7	1.30	0.95
4	+17.3	+7.0	−3	1.60	0.73
5	+9.9	0	+40	1.40	1.10
6	−3.2	0	+3	1.20	.93
7	+6	+4.3	+3	1.40	0.90
8	+8.4	+6.3	+2	1.26	0.80
Average	+5.7	+3.7	+9.5	1.43	0.93

Our next effort is an attempt to correlate *x*-ray findings with groups of clinical cases studied also with great care by the usual methods of examination. The type of chronic valvular heart disease offering the greatest clinical difficulty in arriving at a positive diagnosis is undoubtedly mitral regurgitation. If *x*-ray methods are to offer any great help in chronic valvular heart disease, most should be expected of them in this condition. Cases examined were carefully selected on the basis of absence of symptomatology and absence of anything in the history suggesting any degree of cardiac incompensation now or in the past; in other words, cases truly representative of chronic valvular heart disease as distinct from acute or subacute heart disease. Application of these strict criteria throws many cases out of consideration. The *x*-ray examinations included in all cases a frontal teleroentgenogram by Bardeen's technic, frontal orthodiagram, lateral orthodiagram with examinations of the retrocardiac space and posterior contour of

the left auricle and ventricle and finally a special procedure of measurement of displacement of the cardiac shadow on shifting the tube a known distance in an effort to estimate the development of the heart in depth. The last requires further explanation. Vaquez and Bordet[11] suggested a measurement of the apparent left border of the heart on shifting the tube 10 cm. horizontally. If the position of the target in relation to the screen and the position of the heart in relation both to the target and screen are constant, the apparent displacement of the border will obviously vary with the development of the left ventricle posteriorly. Vaquez and Bordet controlled the position of the target in reference to the screen, using a distance of 60 cm., but apparently made no effort to control the relation of the heart to either target or screen. They found in normals a displacement of 7 to 14 mm. under these conditions; considerably increased in left ventricular hypertrophy. This method has also been used by Morison and White.[12] A consideration of the geometry of the situation shows that a variation in position of the heart will cause an equal variation of this displacement. We have, therefore, modified this technic in the following way: We pay no attention to the position of the screen or heart but measure the displacement on both right and left sides and express the results as a ratio, namely, as the displacement of the right contour divided by the displacement of the left contour. Measurements are made at the widest points of the two contours. Since the ventricles in cross-section in the normal heart represents an approximate ovoid somewhat thicker on the right, the right displacement is normally greater and the ratio above unity. Enlargement of the left ventricle posteriorly or even of both ventricles because of the position of the right auricle in forming the right contour should cause the displacement on the left to approximate or exceed the right and the ratio to approach or fall below unity. This, we believe, we have found to be the case and that this method is promising in estimating degrees of hypertrophy which perhaps fall within the normal range in the frontal teleroentgenogram or orthodiagram. Finally, it is to be noted that in our tabulations of area of the frontal silhouette we have used Bardeen's tables for comparison with the normal average.

The clinical group in which we have been most interested is mitral regurgitation. Table IV shows 5 cases, carefully selected according to the criteria mentioned above, and in which we also believed represented diagnosis of this condition, with which any clinician must agree. The teleroentgenogram shows an average increase of 24 per cent in area and of 12 per cent in diameter; the retrocardiac space was reduced in all; the R/L ratio averaged 0.77. In Table V, 12 cases are tabulated in which we felt that the general clinical picture was sufficient to make a diagnosis of mitral regurgitation, but in no case presenting that combination of findings

TABLE IV.—GROUP 1, MITRAL REGURGITATION

Group of cases showing (1) history of acute rheumatic fever;(2) definite enlargement to percussion of symmetrical type; (3) typical murmur; (4) accentuated pulmonic second sound.

Subject.	Apex-beat.	Teleroentgenograph		Retrocardiac space.	Depth ratio.	Electrocardiogram.
		Area.	Transverse diameter.			
1	Out	+41	+17	Reduced	.97	L.V.P.
2	Normal	+28	+20	Oblit.	.59	Normal
3	Out	−7	+2	Oblit.	.71	Normal
4	Out	+35	+14	Oblit.	.71	L.V.P.
5	Out	+22	+6	Reduced	.88	Normal
Average		+24	+12		.77	

Summary: 5 cases: apex-beat out in 4, normal in 1. Teleroentgenograph area above normal range (10 per cent) in 4, transverse diameter above normal range in 3. Retrocardiac space reduced in all. Depth-ratio range, 0.59 to 0.97. Electrocardiogram normal in 3, L.V.P. in 2.

characteristic of the preceding. It is entirely probable that some of these cases were not mitral regurgitation. The average cardiac area and diameter is within the usually recognized normal range, although slightly increased above the average. The retrocardiac space is reduced in 9 cases, or 75 per cent; the average R/L ratio is 1.15. The next group (Table VI) comprises 21 cases in which we felt an absolutely positive diagnosis could not be made, either as normal or as mitral regurgitation. These show approximately the same increase in cardiac area as the preceding, no average increase in transverse diameter; the retrocardiac space is reduced in 5, or 24 per cent; the R/L ratio is 1.53. The next group (Table

TABLE V.—GROUP 2, CLINICAL DIAGNOSIS OF MITRAL REGURGITATION

Subject.	Acute rheumatic fever.	Apex-beat posit.	Enlarged to percussion.	Teleroentgenogram.		Murmur.	Retrocardiogram space.	Depth R/L	P^2	Electrocardiogram.
				Area.	T. D.					
1	Yes	Out	Mod. Sym.	+7	+5	Typical	Reduced	0.72	Ac.	Normal.
2	Chronic?	Out	Slight	+14	+15	Typical	Reduced	1.5	Ac.	None.
3	Yes	Normal	Moderate	+11	0	Typical	Normal	1.6	N.	None.
4	Yes	N. V.	Mod. Sym.	−11	+4	Typical	Normal	1.22	Ac.	None.
5	No	Normal	Slight	+19	+3	Typical	Oblit.	0.76	Ac.	L.V.P.
6	Yes	Out	No	+10	+10	Typical	Oblit.	1.08	Ac.	Normal.
7	Yes	Out	Moderate	+1.6	+8	Atypical	Oblit.	1.10	N.	Normal.
8	No	Normal	Normal	+16.0	+1.5	Typical	Oblit.	2.0	N.	Normal.
9	No	Normal	Normal	−1	−3	Typical	Reduced	0.7	N.	None.
10	Yes	Normal	Normal	+15	+4	Typical	Normal	0.8	N.	None.
11	Repeated	Normal	Normal	+10	+4	Typical	Reduced	1.2	N.	None.
12	Yes	Normal	Normal	+4	+9	Atypical	Reduced	1.2	Ac.	Normal.
Average				+8	+5			1.15		

Summary: 5 cases. Acute rheumatic fever in 8. Apex displaced in 4. Cardiac enlargement to percussion in 6, to *x*-ray (above 10 per cent) in 5. Transverse diameter above normal range in 1. Murmur typical in 10. Retrocardiac space reduced in 9. Pulmonic second sound accentuated in 6. Electrocardiogram: None made in 6, normal in 5, left ventricular preponderance in 1. Depth ratio varies between 0.7 to 2.0. Below 1.78 in 11. Below 1.53 in 10. Below 1.15 in 6.

TABLE VI.—GROUP 3, MITRAL REGURGITATION. DOUBTFUL CLINICAL GROUP

Subject.	Acute rheumatic fever.	Apex-beat posit.	Enlarged to percussion.	Teleroentgenogram.		Murmur.	Retrocardiogram space.	Depth R/L	P^2	Electrocardiogram.
				Area.	T. D.					
1	Yes	Normal	Slight Inc.?	+21	−1	Atypical	Normal	1.7	N.	Normal.
2	No	Normal	No	+1	−11	Typical	Reduced	0.95	N.	None.
3	No	Normal	No	+5	−2	Atypical	Normal	1.13	N.	Sl. R.V.P.
4	No	Normal	No	+1	+3	Atypical	Normal	2.2	Ac.	Normal.
5	No	Normal	No	+6	+7	Typical	Normal	1.05	Ac.	None.
6	No	Normal	No	+15	−5	Typical	Normal	1.4	Ac.	L.V.P.
7	No	Normal	No	+4	−11	Typical	Normal	2.5	N.	Normal.
8	?	Normal	Moderate	+16	−1	Atypical	Normal	2.6	N.	L.V.P.
9	No	Out	Moderate	+25	+8	Atypical	Normal	2.1	N.	None.
10	No	Normal	No	−4	−4	Typical	Normal	2.4	N.	R.V.P.
11	Yes	Normal	No	0	−2	Atypical	Normal	1.6	N.	Sl. R.V.P.
12	No	Out	No	+11	+7	Typical	Reduced	0.61	N.	Normal.
13	No	Out	Slight	−4	+4	Typical	Normal	1.75	N.	Normal.
14	?	Normal	Normal	0	+3	Atypical	Normal	1.2	N.	Normal.
15	No	Normal	Slight	+10	+5	Atypical	Normal	1.56	N.	None.
16	No	Normal	Slight	+15	+12	Atypical	Reduced	1.2	N.	None.
17	No	Normal	No	0	−9	Typical	Oblit.	0.83	N.	Normal.
18	No	Out	Moderate	+15	+6	Atypical	Normal	1.6	N.	Normal.
19	No	Out	No	+12	0	Atypical	Normal	1.6	N.	R.V.P.
20	Yes	Normal	No	−11	−1	Atypical	Reduced	1.1	N.	Normal.
21	No	Normal	No	+15	−5	Typical	Normal	1.4	Ac.	L.V.P.
Average	....	.....	.....	+7.3	0	.....	.....	1.53		

Summary: 21 cases. History of acute rheumatic fever positive in 3, questionable in 2. Apex-beat abnormal in position in 5. Cardiac area increased to percussion in 7. Teleroentgenographic area 10 per cent or more above normal in 10. Transverse diameter above normal range in 2. Murmur typical in 9. Retrocardiac space reduced in 5. Depth ratio ranges between 0.83 and 2.6, with average of 1.53. 17 below 178, 6 below 1.15, none below 0.77. Electrocardiograms in 16 cases, 9 normal, 4 show right ventricular preponderance, 3 left ventricular preponderance. P^2 accentuated in 3.

TABLE VII.—GROUP 4, PROBABLE ACCIDENTAL CARDIAC MURMURS

Subject.	Acute-rheumatic fever.	Apex-beat posit.	Enlarged to percusssion.	Teleroentgengram.		Murmur.	Retrocardiac space.	Depth R/L	P^2	Electrocar-diogram.
				Area.	T. D.					
1	No	Normal	No	+4	−4	4th I.S.	N.	1.4	N.	None.
2	No	Normal	No	+7	−7	Apical	N.	2.7	N.	Normal.
3	No	Normal	No	+3	0	Apical	N.	1.47	N.	Normal.
4	No	Normal	No	−18	−20	C. Resp.	N.	1.6	Ac.	Normal.
5	No	Out	No	+7	+2	After Ex.	N.	1.85	N.	None.
6	No	Normal	No	−15	−17	Apex	N.	1.86	N.	None.
7	No	Normal	No	−6	0	Recumbent only	N.	1.5	N.	Normal.
8	No	Out	No	+2	+12	3d L.I.S.	N.	1.22	N.	None.
9	No	Normal	No	−9	−15	Apex	N.	1.9	N.	R.V.P.
10	No	Out	No	+11	+12	Recumbent	N.	1.2	N.	Normal.
11	No	Normal	No	+9	+4	Apex	Reduced	2.7	N.	None.
12	No	Normal	No	+9	−2	Recumbent	N.	1.3	N.	Normal.
13	No	Normal	No	+8	−6	Recumbent	N.	1.3	N.	Normal.
14	No	Normal	No	−20	−25	Recumbent	N.	1.6	N.	Normal.
15	No	Out	No	+2	−3	Recumbent	N.	2.3	N.	Normal.
16	No	N.P.	No	−5	+6	3d L.I.S.	N.	1.25	N.	Normal.
17	?	Normal	No	+7	−5	4th L.I.S.	N.	2.65	N.	R.V.P.
18	No	Normal	No	+6	−4	C. Resp.	N.	1.83	N.	Normal.
19	No	N.P.	No	+2	−5	Recumbent	N.	1.33	N.	None.
20	No	Normal	No	+3	−6	Recumbent	N.	1.7	N.	Normal.
21	No	Normal	No	−16	−8	3d L.I.S.	N.	1.8	N.	Normal.
22	No	Normal	No	−15	−16	Apex	N.	2.1	Ac.	None.
23	No	Normal	No	0	−6.5	Recumbent	N.	2.65	N.	Normal.
24	No	Normal	No	+20	+3	Recumbent	N.	1.45	N.	Normal.
Average				+0.4	−4.4			1.76		

Summary: 24 cases. No history of acute rheumatic fever in 23, questionable history in 1. Apex outside midclavicular line in 4, within midclavicular line in 18, not visible nor palpable in 2. Cardiac area normal to percussion in all. Two cases show a teleroentgenogram area more than 10 per cent above the average and in one case the transverse diameter is also increased more than 10 per cent. The murmur was apical in 6, was present only in the recumbent position in 9 and was definitely cardiorespiratory in 2. The depth ratio varied between 1.2 and 2.7. The average was practically equal to the average in the normal series. Ten cases fell below 1.53 and none below 1.15. Electrocardiograms in 17, normal in 15, R.V.P. in 2.

VII) comprises 24 cases classed clinically as accidental murmurs. We should like to emphasize that the clinical classification in all these cases was made independent of the *x*-ray findings. These showed an approximately normal average area and transverse diameter while the retrocardiac space was reduced in one, or 4 per cent. The R/L ratio averaged 1.76. The next group (Table VIII) comprises a carefully selected normal group. The average areas and transverse diameters are practically normal, the retrocardiac space is reduced in 3, or 12 per cent; the R/L ratio is 1.78, practically the same as in the accidental murmur group.

TABLE VIII.—GROUP 5, NORMAL GROUP

No history of acute rheumatic fever or severe tonsillitis. Apex in 5th interspace within midclavicular line. Cardiac area normal to percussion. No murmurs. Pulmonic second sound not accentuated. Normal arterial blood-pressure. No associated disease.

Subject.	Teleroentgenograph area compared with normal for subjects in per cent.	Greatest transverse diameter compared with normal in per cent.	Retrocardiac space.	Depth ratio R/L	Electrocardiograms.
1	−9	−4	N	1.5	None.
2	+7.5	+4	N	1.5	None.
3	+9.2	0	N	1.33	Normal.
4	0	+3	N	1.75	Normal.
5	−6	+10	N	1.2	Normal.
6	+10	+3	N	1.5	Sl. R.V.P.
7	−6	−13	N	1.4	None.
8	−24	−23	N	2.0	Normal.
9	−4	−11	N	3.5	None.
10	0	−8.5	N	1.6	R.V.P.
11	0	+5	N	1.7	L.V.P.
12	+22	+15	N	2.1	Normal.
13	−9.5	−1	N	2.3	None.
14	+8.2	+15	N	2.0	None.
15	+1	−5	N	1.6	None.
16	+17	−6	Much reduced	1.08	None.
17	+4	−9	Reduced	1.35	None.
18	−17	−6	N	1.66	Sl. L.V.P.
19	+18	+8	N	2.0	None.
20	+15	−1	N	1.9	None.
21	+7	+1	N	1.3	Normal.
22	+8	0	N	1.36	None.
23	+2	−6	Slightly reduced	3.0	None.
24	+10	+5	N	2.0	None.
Average	+3	−1.2		1.78	

Summary: Cardiac area above normal (10 per cent) in 3, below normal in 1. Transverse diameter above normal range in 2, below in 1. Retrocardiac space normal in 21, reduced in 3. Lowest depth ratio 1.08, highest 3.5. Ratio below average in 15, above in 9. Ratio above 1.15 in 23. Electrocardiograms in 10, normal in 6, R.V.P. in 2, L.V.P. in 2.

TABLE IX.—SUMMARY—MITRAL REGURGITATION SERIES

Group.	Designation.	No. of cases.	Percentage of total cases.						R/L ratio.					
			Enlarged to percussion.	Enlarged to teleroent. (10 per cent).	P^2 accent.	Murmur typical.	Lower retro. space reduced.	History of ac. R.F.	Average.	Range.	Below 1.78	Below 1.53	Below 1.15	Below 0.77
1	Definite	5	100	80	100	100	100	100%	0.77	0.59–0.97	100%	100%	100%	66%
2	Probable	12	50	42	50	83	75	66	1.15	0.70–2.0	92%	83%	50%	25%
3	Doubtful	21	33	48	14	43	24	14–24	1.53	0.83–2.6	84%	48%	30%	0
4	Accidental	24	0	8	8	12	4	0–4	1.76	1.20–2.7	54%	42%	0	0
5	Normal	24	0	12	0	...	12	0	1.78	1.08–3.5	62%	42%	4%	0
						MISCELLANEOUS								
6	Mitral stenosis and regur.	7	100	57 (Avg. + 19%)	59	...	86	43	1.55	0 91–2.7	71%	57%	29%	0
7	Mitral stenosis	7	29	14 (Avg. + 4%)	57	...	57	29	1.22	0.56–1.47	100%	100%	29%	14
8	Aortic regurg.	9	100	100 (Avg. + 27%)	44	...	89	56	1.29	0.68–2.3	89%	78%	44%	11
9	Aortic and mitral regurg.	7	100	86 (Avg. + 28%)	29	...	86	29	1.25	0.60–3.10	86%	86%	71%	14

These groups are finally summarized in Table IX. Under R/L ratio there is given the average, the range and the percentage in each group that falls below the averages of the normal, accidental, doubtful, probable and definite groups. Groups of other chronic valvular conditions are also summarized for comparison.

It would seem clear that the clinical value of cardiac mensuration has distinct limitations. In suspected early mitral regurgitation, where so much depends upon an accurate estimation of the size of the organ, the departure from the average normal is not sufficient to be of much assistance, and, indeed, may be misleading if too much stress is placed upon it. In our opinion it has not the value of careful estimation of the size and activity of the heart by the usual methods of physical examination, the position and character of the apex-beat and accurate percussion of the cardiac contour. If this is done by a competent worker the frontal teleroentgenogram or orthodiagram is of value as a confirmatory procedure. Each of these methods has its advantages, but the great advantage of the orthodiagram, in our opinion, is the view it gives of the moving heart and the possibility of special mensuration and examination in the lateral position. The shadow of the moving heart can be frequently seen through the shadow of the diaphragm—rarely possible in the *x*-ray film—and this aids in the more accurate completion of the frontal contour. Lateral *x*-ray films are successful only with very careful technic. Efforts with the orthodiagraph method to estimate changes in development of the heart not recognizable in the frontal plane we believe to offer considerable promise; but here, again, too much stress must not be given to such determinations, and they should be regarded merely as part of a series of data upon which the diagnosis is based. Diagnosis in early chronic valvular heart disease is thus a matter of inference from a number of types of observation, and the information derived from *x*-ray studies must be regarded in this light. For this additional information that they may give in doubtful cases, it is our conviction that *x*-ray methods, especially orthodiagraphic study, should be applied to all such cases. Wilson and Merrill,[13] in a recent paper, suggest that interpretation of the *x*-ray findings should be made by the one who is responsible for the diagnosis

rather than the roentgenologist. We should like to go a step further and state our conviction that the fluoroscopic examination should be made by the clinician. Impressions from such an examination may be of as much or more value as the data obtained from mensuration.

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DISCUSSION

Prof. Wenckebach, Vienna: The form of the orthodiagram depends essentially on the level of the diaphragm. For my students I compare the mass of the heart with that of a sack of peas. If there is no base for the sack to rest on it takes a pendent shape with small horizontal diameter, but if it is supported its base follows the shape of the base upon which it is resting—it will become wider and flatter at the base with large horizontal diameter. That is the same with the heart. I am an active radiograph man, but I am skeptical of the value of gauging the bulk of the heart by means of figures. I am trying to get as much as possible out of the orthodiagram, but also as much as possible out of percussion, which may also be of value in trying to gauge the position of the under side of the heart, because although we may be able to trace the rest of the outline, a most important part of the figure is always lacking. In order to make visible this lower surface of the heart, I tried letting oxygen into the abdomen, but the attempt was not successful, although the method was a perfectly safe one as regards the patient. The reason is this: By admission of air into the abdomen the heart is pushed up and backward by the air bubble and it is impossible to see the normal underside of the heart on the *x*-ray

screen. This led me to go back to the older method of careful percussion by which you can follow the underside of the heart by marking the absolute dulness of the heart even through the liver dulness. In the long pendent heart there is a type of line different from that in the high heart which is much more horizontal. This gives you an idea how high the heart is lying in the chest. When there is great enlargement of the left ventricle in mitral or aortic incompetence there is an enormous increase of the left ventricle which you can detect in no other way. I believe this method is helpful.

Dr. W. S. Thayer, Baltimore: One must have had years of constant practice in percussion of hearts in order to appreciate its value. I am rather surprised to hear Dr. Pratt state that he values the orthodiagraphic methods so highly. In comparing my estimates of the size of the heart by percussion with the measurements by orthodiagrams, I find that I have rarely undervalued the size of the heart. The tendency is to overestimate its size because of the convexity of the chest, an overestimation for which due allowance is easily made. Orthodiagraphy is a valuable method of precision, an important addition to our diagnostic methods, but it does not take the place of percussion. The practitioner who cannot rely on his cardiac percussion is in a sadly helpless position. Every effort like that of Dr. Eyster's is valuable, but such information should not lead men to give up methods that are the basis of the practice of medicine. One of the few satisfactions of growing a few years older is that one learns with time to use his fingers better. I have yet to learn a single method of physical examination that will give me such valuable information of the size of the heart as does the use of my fingers.

Dr. Henry Sewall, Denver: The value of *x*-ray methods depends a good deal on the interpretation of the pictures. I was struck by a sentence in an article by Dunham in which he asserted that it was a matter of extreme importance in *x*-ray work on the lungs to study the picture *before* examination of the patient. I had usually done the opposite. We must admit that it is easy to read into a picture findings we think we have obtained by physical examination. The error from the personal equation is likely to be less if the picture is studied first. That may apply to the *x*-ray of the heart; it may be useful to study the *x*-ray first and then make the clinical examination.

Prof. Wenckebach: May I be permitted to add a word in closing? Percussion certainly is the most difficult art in physical diagnosis. In my case it has taken many years of practice before I could be sure of being halfway exact. I object to looking at the *x*-ray picture before percussing, because when I know its form I make a most beautiful percussion. Look-

ing at the picture first spoils your percussion. If you want to keep up a high standard of percussion you should do it first.

Dr. Eyster (closing): I do not mean to give the impression that we regard *x*-ray methods of no value in the diagnosis of chronic valvular heart disease. The present study is on selected early cases and concerned with frontal-plane projection of the heart. Here the *x*-ray findings may be misleading and too much attention may be paid to them. Their real value seems to be largely confirmatory of other findings. I agree entirely with Dr. Thayer in regard to cardiac percussion.

Dr. Joseph H. Pratt, Boston: May I be permitted to correct an impression: I have always been an advocate of cardiac percussion, and I do not want to be put on record as underestimating its value.

Dr. J. B. Herrick (president), Chicago: In regard to the question as to whether or not clinical examination should precede the examination of the *x*-ray picture, I am reminded of a sentence from Cæsar's *Commentaries* in which it is said, "Men believe to be true what they wish to be true." That general principle holds in this matter.

THE PHYSICAL FINDINGS IN PERICARDITIS WITH EFFUSION[1]

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The diagnosis of a pericardial effusion is often a matter of great difficulty. Even with the most painstaking physical examination a large effusion may be missed, as all clinicians who follow their patients to the autopsy table realize. This fact indicates that the physical signs of pericardial effusion are not always distinctive and led one of the writers (R. S. M.) and Bader[2] to study the problem experimentally.

In these experiments, ascitic fluid was injected into the pericardium of fresh cadavers within four hours after death. Particular attention was paid to the shape of the cardiohepatic angle and to the shape and extent of the relative cardiac dulness and the cardiac shadow in radiograms. It was found that the cardiohepatic angle is acute—at the most a right angle, but never obtuse in the injected pericardia—even after the introduction of 2 liters of fluid. The least amount of fluid causing a change in the percussion findings was 250 cc (inconstant), but it was not until 500 cc had been injected that definite percussion and *x*-ray changes could be detected with uniformity. It was further observed in the experimental injections that there is a marked widening of the retromanubrial dulness at the base of the heart, with a corresponding increase in width of the

[1] From the Medical Clinic and the Roentgenologic Laboratory of the Cincinnati General Hospital.

[2] A Comparison of the Percussion and Roentgen-ray Findings after Injection of the Pericardium, Jour. Am. Med. Assn., 1917, lxix, 450.

shadow in the radiograms, and, what is probably of greater practical importance, that the area of dulness and the extent of the shadow in this region decrease in width when the cadaver is changed from the recumbent to the erect posture.

The present report is the result of a continuation of the earlier work, but instead of cadavers we have confined our observations to patients ill with pericarditis.

Our attention has been focussed again chiefly on the percussion findings, though we, like others, have been impressed with the fact that, even with large accumulations of fluid in the pericardium, the apex impulse may remain visible and palpable and the heart sounds of good intensity throughout the course of the disease; and that, at times, a pericardial friction rub may persist along the left sternal border, near the base of the heart.

FIG. 1.—Teleroentgenogram pericarditis with effusion.

In many of the text-books on diagnosis the statement is made that the cardiohepatic angle becomes obtuse as fluid accumulates in the pericardium. In the past two and a half years we have found the angle to be acute, both by percussion and by roentgenologic examination (teleroentgenograms and fluoroscopy), except in a few instances in which a right angle was determined (Figs. 1, 2 and 3). In no instance was the angle obtuse. The percussion was carried out with the eyes averted or closed; direct percussion, using the second finger, was employed. The shape of the angle has been

practically unaffected by changing the patient from the recumbent to the erect posture.

The shape of the area of relative cardiac dulness is a matter of considerable interest. It is pear-shaped, except when pericardial adhesions or extrapericardial lesions interfere with the distention of the sac by the fluid. There is an early increase of the cardiac dulness both to the right in the third and fourth interspaces and to the left beyond the apex. This is more marked when the patient assumes the erect posture and there is a corresponding change in the fluoroscopic shadow.

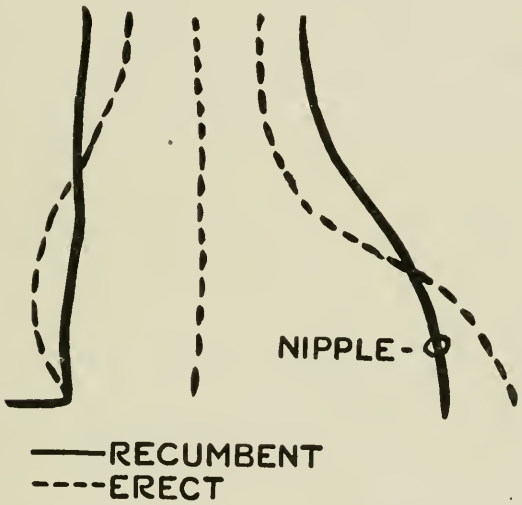

FIG. 2.—Pericarditis with effusion. Relative cardiac dulness in the recumbent (continuous line) and erect (broken line) postures.

Of greater practical importance, in our experience, has been an extension of the relative dulness upward in the first and second interspaces. In this connection the fact may be recalled that the pericardium extends along the great vessels for a distance of one and a half to two inches from their point of origin in the heart—the entire ascending aorta is within the pericardium. An early filling of these cul-de-sacs, as evidenced by an increase in the width of the area of dulness and of the shadow when the patient is recumbent, is one of the most important physical signs of a pericardial effusion.

If the dull area and shadow become narrower when the patient is erect it is indicative of fluid. Thus far we have encountered this physical sign only in connection with pericardial effusion and have not failed to demonstrate fluid when shifting retromanubrial dulness was found (Fig. 2). Thus, our clinical studies confirm the results obtained experimentally.

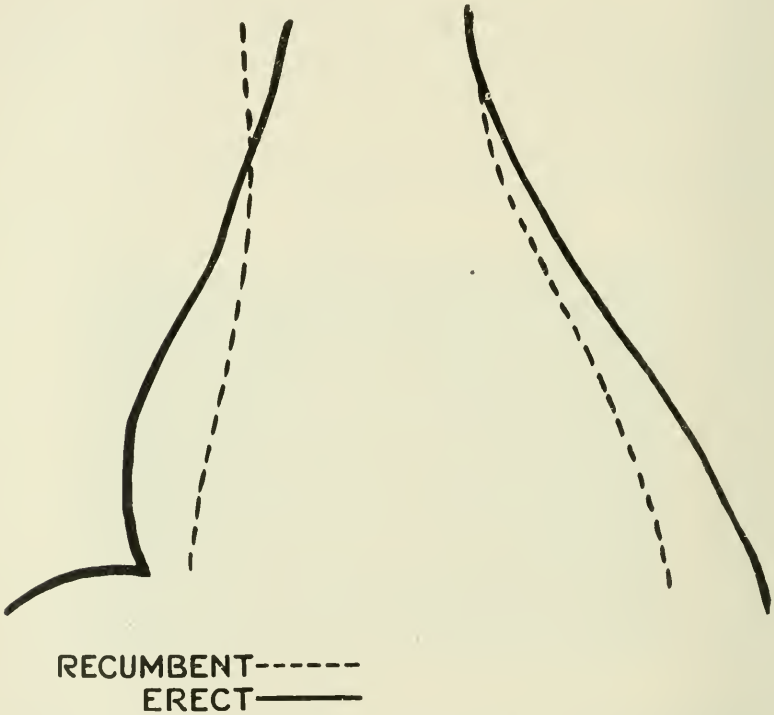

Fig. 3.—Pericarditis with effusion. Fluoroscopic tracing of the cardiac shadow in the recumbent (broken line) and erect (continuous line) postures. (Note. The findings recorded in Figs. 2 and 3 are not from the same patient.)

The absence of visible pulsation has been noted fluoroscopically repeatedly with large effusions and has been an aid in the differentiation of this condition and cardiac dilatation. With smaller effusions a slight pulsation may be observed.

Dulness in the left back near the angle of the scapula, with bronchial breathing, pectoriloquy and bronchophony or egophony, at

times with diminished breath sounds and decreased tactile fremitus, noted by many observers, has proved a helpful sign with large effusions. In one instance the extent of the dull area was so great that pleural effusion was diagnosed, but aspiration and subsequent study made it altogether probable that the pericardium had been aspirated.

Conclusions. 1. The cardiohepatic angle in pericardial effusion is usually an acute angle.

2. The area of relative cardiac dulness in effusion is pyriform and generally extends upward to the first interspace.

3. Widening of the area of dulness and of the shadow in the first and second interspaces occurs relatively early in effusion and is best determined with the patient in the recumbent posture.

4. Shifting dulness (*i. e.*, a narrowing of the dull area, with a corresponding decrease in width of the shadow over the great vessels when the patient is changed from the recumbent to the erect posture) has proved to be the most reliable physical sign of fluid in the pericardium.

5. Widening of the dull area and of the shadow to the right and to the left above the diaphragm when the patient is erect is found with fluid.

6. There is an absence or marked decrease of visible pulsation in the shadow fluoroscopically in pericardial effusion.

7. Dulness at the angle of the left scapula is often present with a large accumulation of fluid in the pericardium.

DISCUSSION

Dr. Emanuel Libman, New York: One of the *x*-ray pictures shows a point which is sometimes valuable in the diagnosis of effusion as contrasted with dilatation—namely, a bending inward near the upper part of the left border of the cardiac outline. This can occasionally be made out by percussion.

Dr. L. A. Conner, New York: The recognition of small amounts of fluid in the pericardium seems to me a very difficult matter. The first recognizable sign is apt to be the appearance of flatness behind and to each side of the manubrium and above the normal cardiac dulness. My experience is that the signs with respect to the cardiohepatic angle vary greatly in different cases. They are usually those indicated by Dr. Morris, but

there are frequent exceptions to that rule. I feel strongly that even very large effusions are often overlooked because of the widespread belief that the existence of a pericardial friction sound is not compatible with any considerable amount of liquid in the pericardium. That belief is certainly not justified. The friction sound is often present even when the effusion is enormous. I should like to emphasize the importance of the posterior signs in cases of large effusion. They are constant and trustworthy signs, but are often interpreted as those of pleural effusion or of pneumonia.

Dr. W. S. Thayer, Baltimore: One of the points of importance which Dr. Morris emphasized is the change of dulness at the base with change of position. We have all observed change in the shape of dulness with change of position from side to side, but the change in the amount of dulness at the base in the erect and recumbent postures is of more importance. I have already mentioned one case of this nature before this Association—a case in which the weight of the fluid in the erect posture caused evident compression of the superior cava. Here the change in outline of the cardiac dulness with change of position was extraordinary.

Dr. Warren Coleman, New York: My experience is contrary to that of Dr. Libman. I have found that flattening of the angle formed by the great vessels and the left border of the heart, as obtained by percussion, is one of the earliest signs of pericardial effusion. Dr. Morris' *x*-ray pictures, I think, bear out this opinion.

Dr. F. T. Lord, Boston: Contrary to Dr. Coleman, I have had great difficulty in the determination by percussion of the obtuse angle of junction between the mediastinal and cardiac dulness at the left of the sternum, and an elevation above its normal position of the upper limit of cardiac dulness to the left of the sternum has seemed of more value in suggesting the presence of pericardial effusion. With Dr. Conner, I would emphasize the diagnostic value of signs of a circumscribed area of atelectasis with patent bronchi in the left back. This is especially helpful in diagnosis in the more difficult cases where the heart is held close to the anterior chest wall by adhesions and the pericardial effusion is largely in the posterior part of the sac. It should be appreciated in estimating the value of this sign that similar findings in the back may be present in rare instances, especially in children with much enlarged hearts without pericardial effusion.

Dr. Morris (closing): I think it may be appreciated in very large effusions. There is also an apex impulse in large effusions. The posterior signs are important; we have a patient at the present time with pericardial effusion and dilated heart, with adhesion at both borders. There is shifting dulness at the base of the heart and an area at the lower left border with signs of bronchial breathing. The fluid is located posterior to the heart.

THE BEHAVIOR OF THE HEART IN EXOPHTHALMIC GOITER AND ADENOMATOUS GOITER WITH HYPERTHYROIDISM[1]

By FREDERICK A. WILLIUS, M.D.,
(By Invitation)
AND
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With a Note on the Pathology

By LOUIS B. WILSON, M.D.
ROCHESTER, MINN.

The present study[2] was undertaken for the purpose of determining what factor or factors in exophthalmic goiter and in adenomatous goiter with hyperthyroidism are contributory in producing the cardiovascular phenomena so characteristic of these diseases. Observations were made on a consecutive series of 377 patients with these diseases, including electrocardiograms, the out-patient and hospital periods, the complete histories, physical examinations, daily notes and repeated blood-pressure, pulse-rate and basal metabolic-rate determinations. The electrocardiograms, blood-pressure and other observations were obtained, as a rule, either before or promptly after patients were admitted to the hospital, at frequent intervals thereafter, and also after operative procedures and before dismissal from observation.

As shown in Table I, it was found that in both exophthalmic goiter and in adenomatous goiter with hyperthyroidism the pulse

[1] Mayo Foundation and Mayo Clinic.

[2] Presented here in abstract. Complete data and bibliography are published in Medical Clinics of North America, July, 1923.

pressure is increased beyond normal. In exophthalmic goiter the increase in pulse pressure is effected by a moderate increase in the systolic pressure with a normal or slightly lowered diastolic pressure. In contrast, the systolic pressure in adenomatous goiter with hyperthyroidism is higher, with a correspondingly greater diastolic pressure. In the latter condition, distinctly high diastolic blood-pressures are more commonly encountered than in exophthalmic goiter.

AVERAGE BLOOD-PRESSURE OBSERVATIONS ON 377 PATIENTS WITH EXOPHTHALMIC GOITER AND ADENOMATOUS GOITER WITH HYPERTHYROIDISM[1]

	Out-patient:		Entrance:		Discharge:	
	Exophthalmic goiter.	Adenomatous goiter.	Exophthalmic goiter.	Adenomatous goiter.	Exophthalmic goiter.	Adenomatous goiter.
Systolic	147	153	131	139	128	129
Diastolic . . .	73	83	72	78	75	76
Pulse pressure . .	74	70	59	61	53	53
Pulse rate . . .	123	110	103	97	96	94

In view of the constant elevation in the basal metabolic rate in exophthalmic goiter and in adenomatous goiter with hyperthyroidism, it is obvious that there must be an increase in the rate of circulation to meet the increased demand of the tissues for the transportation of metabolites. The first effect of the increased demand is acceleration of the heart-rate, soon followed by an increase in the volume outflow per beat. In the absence of aortic disease the increase in pulse pressure, provided the diastolic pressure is not greatly increased, is evidence of this increased output per beat. The rarity of an increased diastolic pressure in exophthalmic goiter shows that in this disease hypertension is not a common complication; on the other hand, the frequent observation of an increased diastolic pressure in adenomatous goiter with hyperthyrodisim shows that this disease is often associated with hypertension.

[1] These figures represent averages of several determinations on many patients, and are therefore of much greater significance than if they were single observations on individual patients.

Cardiac murmurs occurred in nearly half of the cases in the series. In only 2 instances were the murmurs due to endocardial valvular disease. The murmurs not of endocardial origin were of two types: The first, systolic in time and blowing in character, has its point of maximal intensity at the third left intercostal space and is usually quite localized; this murmur is possibly associated with changes in the blood flow, as it disappears with a slowing of the circulation rate as the disease is arrested. The second murmur, also systolic and blowing in quality, has its point of maximal intensity at the apex and has a variable transmission; it is probably due to mitral regurgitation secondary to dilatation of the left ventricle.

Edema of the lower extremities occurred in about one-fifth of the patients. It disappeared promptly after their admission to the hospital except in the 9 patients in whom the cardiac insufficiency was extreme.

Digitalis was administered to 35 per cent of the patients with exophthalmic goiter and to 41 per cent of the patients with adenomatous goiter with hyperthyroidism. The pulse pressure was elevated from 62 to 65 mm. in cases of exophthalmic goiter and from 59 to 65 mm. in cases of adenomatous goiter, with hyperthyroidism, and an average slowing in the pulse-rate of four beats each minute was noted in cases of exophthalmic goiter and fifteen beats each minute in cases of adenomatous goiter with hyperthyroidism. The effect of digitalis on the heart-rate was more marked in patients exhibiting auricular fibrillation than in those with regular rhythm.

Five of the patients in the series died following operation for exophthalmic goiter and 2 died who were not operated on, and 3 patients with adenomatous goiter with hyperthyroidism died following thyroidectomy; none of these died from cardiac failure; We also reviewed an additional 13 deaths before and after those occurring in this series, making a total of 23 consecutive deaths, and in only 1 instance could death be attributed to cardiac failure. This patient had general anasarca, was dyspneic and cyanotic, the auricles were fibrillating and the heart was markedly enlarged.

Patients who, subsequent to operation, become dyspneic, cyanotic

and hoarse and develop dysphagia with nasal regurgitation of fluids, usually accompanied by increased heart-rate, are sometimes erroneously believed to die of heart failure; this mistake is most common if respiratory obstruction is slight. Careful clinical differentiation reveals that the cardiac phenomena under such conditions are in the main secondary to an anoxemia, often of slight degree, but continued over a considerable time. Asher has demonstrated that animals rendered hyperthyroid by feeding thyroid extract are extremely susceptible even to a slight decrease in the concentration of the oxygen in the inspired air. Partial laryngeal obstruction resulting from injury to the recurrent laryngeal nerve is probably the most common cause of anoxemia. However, we have seen 1 case in which the postmortem evidence was quite definite that an enlarged thymus with slight edema and hemorrhage in the anterior mediastinum probably interfered with the free return of blood to the right auricle.

Auricular fibrillation occurred with about the same degree of frequency in both diseases. In exophthalmic goiter the incidence was 22 per cent, while in adenomatous goiter with hyperthyroidism it was 24 per cent. The cases of auricular fibrillation have been arbitrarily divided for study into three groups, depending on whether it was constant, intermittent or transient.

Constant auricular fibrillation occurred in cases of exophthalmic goiter in 8 per cent (23 patients) and in cases of adenomatous goiter with hyperthyroidism in 10 per cent (8 patients). Intermittent auricular fibrillation occurred in cases of exophthalmic goiter in 5 per cent (15 patients) and in cases of adenomatous goiter with hyperthyroidism in 4 per cent (3 patients). Transient auricular fibrillation was present in cases of exophthalmic goiter in 9 per cent (27 patients) and in cases of adenomatous goiter with hyperthyroidism in 10 per cent (8 patients).

A detailed study revealed that the development of auricular fibrillation did not depend so much on the intensity of the hyperthyroidism, as measured by the basal metabolic rate at the time of observation, as on the duration of the increased metabolic rate in both diseases. In cases of exophthalmic goiter and of adenomatous goiter with hyperthyroidism no appreciable dif-

ferences in the blood-pressure observations were noted if there was associated auricular fibrillation or rhythmic cardiac action. In many instances auricular fibrillation was not present before operation, but developed under the stress of operative procedures. We have observed a few patients who have had emergency operations for other conditions promptly develop auricular fibrillation, and on further study it was found that several of these had had an unrecognized hyperfunctioning adenomatous goiter. The possibility, therefore, of previously unrecognized hyperthyroidism should always be kept in mind in observing patients who suddenly, under stress, develop auricular fibrillation.

Premature contractions and sinus arrhythmia were encountered with average frequency in both thyroid disorders, and have little or no significance.

Paroxysmal tachycardia occurred infrequently. Two patients developed auricular flutter and 3 nodal tachycardia, but in no instance was the condition alarming; the attacks were transient and did not recur.

Among the disorders of cardiac conduction, sinoauricular block occurred in 3 instances, but it was transient and, without exception, insignificant. In 1 case delay in auriculoventricular conduction (*P–R* interval, 0.28 second) occurred during the period of observation and was uninfluenced by atropin. An abberration of the *QRS* complex in all derivations of the electrocardiogram was observed twice in patients with exophthalmic goiter and was not observed in patients with adenoma with hyperthyroidism.

Significant *T*–wave negativity rarely occurred; 3 instances were noted in exophthalmic goiter and 2 in adenomatous goiter with hyperthyroidism.

General Discussion. From a study of the data briefly summarized in this paper and from an analysis of the individual case reports the most outstanding fact is the infrequency, in both exophthalmic goiter and adenoma with hyperthyroidism, of symptoms indicating cardiac disease: Only one-fourth of the patients had auricular fibrillation, and in less than one-half of these was the fibrillation a constant phenomenon; about one-fifth had, as evidence of slight cardiac weakness, a moderate degree of edema of the legs,

which disappeared readily under treatment with rest and digitalis. Not more than 2 per cent of the patients had sufficient clinical evidences of myocardial injury to classify them as having serious cardiac disease. When cardiac damage is present, however, it is a very dominant factor in prognosis and treatment. In this limited group operative mortality can be greatly reduced by measures directed to the restoration and maintenance of cardiac compensation. The misconception of the frequency in hyperthyroidism of cardiac disease undoubtedly arose from interpreting the increased heart-rate as evidence of a pathological condition of the heart, whereas it is evidence of its normal response to the increased demand made on it until the later stages, when the symptom is supplemented by those of fatigue with auricular fibrillation.

The opinion is prevalent that many of the deaths in both diseases are due to heart failure as the major factor. Death is a complex process. It is difficult to estimate the relative importance of the various factors involved, but we believe that our data permit us to do so with more clearness and exactness than heretofore, and possibly to eliminate some misunderstandings on the subject.

Our experience has been that these patients, if they have received appropriate cardiac treatment, apparently do not die of heart failure. In a consecutive series of 23 deaths, including postoperative deaths as well as deaths before operative intervention was possible, there was only 1 in which the heart could be considered as the major contributory cause. This patient had general anasarca, was dyspneic and cyanotic, the heart was markedly enlarged and the auricles persistently fibrillated throughout the period of observation. At no time was operative intervention considered.

Deaths from a postoperative acute hyperthyroid crisis with increasing elevation of the heart-rate, with or without the development of auricular fibrillation, have, as a rule, been considered by the surgeon as due to heart failure. A careful analysis of the symptoms in our series of cases reveals that such an interpretation of death is not in the main justified except for the final cataclysm. The evidence points to the reverse conclusion, because the increased heart-rate is an expression of the attempt of the heart to increase

its volume output sufficiently to meet the demands made on it by the greatly increased metabolism. It is undoubtedly true that the heart muscle, like other tissues in the body, is rendered more irritable and less efficient by the intense thyroid intoxication.

This cardiac reaction closely simulates, although in an exaggerated form, the symptoms seen during the height of a severe acute infection. Because the postoperative hyperthyroid crisis is more prone to occur in patients with a high degree of hyperthyroidism, especially when associated with the irritability, mental instability and depression characteristic of exophthalmic goiter, and because the intensity of the reaction and the number of deaths are decreased by the administration of iodine, as shown by Plummer's recent investigation, it is probable that the reaction is dependent on a peculiar intoxication caused by the presence in the body of an excess of an incompletely iodized thyroid secretion. The intensity of this reaction varies greatly; certain patients barely survive; others might survive provided the heart could withstand the strain even twenty-four hours longer; in this latter sense the condition of the heart must of course be considered as a contributory factor.

From the study of the various data and from an analysis of the individual case reports, especially of patients who died, the conclusion is evident that if the patient is properly treated, cardiac death in exophthalmic goiter and in adenomatous goiter with hyperthyroidism is a very rare occurrence. The finding at necropsy of fatty degeneration of the heart, which in some cases is no more than that found in persons who die of old age, appears to us an expression of the effect of a long-continued or intense toxemia combined with increased activity. Similar changes have been reported in certain voluntary muscles like the quadriceps, and therefore the fatty degeneration of the heart cannot be regarded as the major cause of death, although if extreme it may render the heart unable to withstand the strain until the crisis is past.

The question of surgical mortality in cases of exophthalmic goiter and in those of adenomatous goiter with hyperthyroidism is an expression of the detailed care and coördination of the medical, laboratory and surgical services. Patients with these diseases are very susceptible to anoxemia, and consequently injury to the

recurrent laryngeal nerves and the production of laryngeal edema are particularly dangerous, as they place a still greater load on the already overloaded heart. For the avoidance of these as well as other surgical dangers in the maintenance of a low surgical mortality, the major portion of the credit justly belongs to the surgeons. On the other hand, as we have emphasized, the hearts of patients with exophthalmic goiter and adenomatous goiter with hyperthyroidism are subjected to tremendous demands—demands far in excess of those made in any other disease; in consequence it is incumbent on the physician and the surgeon to aid the heart by appropriate measures of treatment.

Note on the Pathology of the Hearts from the Cases Described by Doctors Willius and Boothby

By LOUIS B. WILSON, M.D.
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The hearts from the cases on which the above clinical report is based are a small group in a large series, the pathology of which I am at present studying. Though the group considered alone is too small and the patients concerned represent too wide a variation in age, continuation and type of disease to warrant conclusions from the pathological data alone, yet the following results of their review may be of interest.

Of the hearts of the 21 cases which came to necropsy, some degree of hypertrophy was noted in 16 instances. This was marked in 2 instances, in which the heart weighed 500 grams and 550 grams respectively. These were both in large females—1 with exophthalmic goiter and the other with nodular goiter which was associated with an acute terminal fibrinous pericarditis. The hypertrophy in the other instances was from 5 to 10 per cent increase in weight. In 2 of the hypertrophied hearts fibrosis was present.

Eleven of the 16 patients with hypertrophied hearts were past forty-five years of age—1 was fifteen, 1 thirty-five and 1 thirty-eight years of age.

Ten of the 16 hypertrophied hearts showed unquestioned dilatation as well as hypertrophy.

No note concerning dilatation or hypertrophy of the heart occurs in the autopsy findings of the other 5 cases except that in 1 instance the heart is noted as weighing 250 grams and being "firm and beefy" in texture. As is usual in exophthalmic goiter the hearts at autopsy were mostly pale, soft and somewhat dilated.

Histologically the myocardium in 18 of the cases shows apparently swollen fibers with indistinct striations and well-marked lipoid changes. However, only 5 of the patients from which hearts were examined were under forty years of age. It is difficult, therefore, to determine accurately whether the lipoid changes were greater than might have been expected in individuals above forty years of age without exophthalmic goiter. It is apparently true, however, that in patients with long-continued, pronounced hyperthyroidism the myocardium shows more advanced fat changes than are present in the myocardium of individuals of the same age without hyperthyroidism.

The pathologist's impression of these hearts, both grossly and microscopically, is that of weak rather than strong muscles, although, as it appears from this series of cases, a large proportion of the hearts show muscular hypertrophy.

DISCUSSION

Dr. George Norris, Philadelphia: I would like to ask if the speaker has had any experience with the use of quinidin therapy in these cases.

Dr. E. B. Krumbhaar, Philadelphia: It would be interesting to know which ventricle is chiefly concerned in this series. Six years ago I reported to this Association the results of an electrocardiographic study of 51 cases of toxic goiter from Dr. Frazier's clinic, studied for the most part before and after operation. There was an equal number of cases showing preponderant hypertrophy in the right and in the left ventricle. After operation, however, the right ventricular preponderance was shown by the electrocardiograph to return usually to normal; but in the case of the left ventricle the preponderance continued unchanged after operation, whether the patients had improved clinically or not. This, I think, is an important distinction in the prognosis as well as in the diagnosis and treatment of this class of patients.

Dr. F. A. Willius (closing): We have not used quinidin in these cases, and therefore I have no experience on that point.

THE DIAPHRAGM EXCURSION AND THE MEDIASTINUM IN LATERAL RECUMBENT POSTURE

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(By Invitation)

In 1921, one of us (G. B. W.), with Forster and Gilbert,[1] published under the title "Postural Rest for Pulmonary Tuberculosis," a report on Roentgen-ray studies of the chest in lateral recumbency.

In 1922, Adams and Pillsbury[2] published an article entitled "Position and Activities of the Diaphragm as Affected by Change in Posture." These authors confirmed our observations as to the wide range of the heart position (the extreme excursion being 6 cm.). They also concluded: "In lateral recumbency the dependent lung is relatively relaxed. Its diaphragmatic ventilation is in excess of that of the upper lung."

Haufbauer and Holzknecht[3] some years ago noted that with a subject lying on one side the half of the diaphragm on the dependent side made a larger excursion and was relatively higher than the upper half. This we confirmed, but we also noted that the increase of excursion of the lower half of the diaphragm does not continue indefinitely but diminishes after an hour or less, and then the excursion of the two halves is approximately the same.

The present contribution deals with a continuation of such observations and confirms fully the fact that after a short time the

[1] Webb, Forster and Gilbert: Jour. Am. Med. Assn., March 26, 1921.
[2] Adams and Pillsbury: Archives of Int. Med., February, 1922.
[3] Haufbauer and Holzknecht: Mitteilungen aus d. Lab. f. radiology. Diagnostik, Heft. 2, Zur Physiologie und Pathologie der Atmung.

diaphragmatic ventilation of the recumbent lung is not in excess of that of the upper lung.

The subjects were studied with the fluoroscope and were all normal normal young men between seventeen and twenty-two years of age:

1. *Subject on right side.*

	At beginning.	After 50 minutes.
Right diaphragm excursion	11 mm.	12 mm.
Left diaphragm excursion	13½ mm.	18 mm.

2. *Subject on right side.*

	At beginning.	After 55 minutes.	After 75 minutes.
Right diaphragm excursion	22½ mm.	18 mm.	18 mm.
Left diaphragm excursion	18 mm.	22½ mm.	22½ mm.

3. *Subject on right side.*

	At beginning.	After 30 minutes.	After 60 minutes.
Right diaphragm excursion	10½ mm.	4½ mm.	4½ mm.
Left diaphragm excursion	9 mm.	10½ mm.	10½ mm.

4. *Subject on right side.*

	At beginning.	After 30 minutes.
Right diaphragm excursion	7½ mm.	7½ mm.
Left diaphragm excursion	9 mm.	16½ mm.

5. *Subject on right side.*

	At beginning.	After 30 minutes.
Right diaphragm excursion	18 mm.	12 mm.
Left diaphragm excursion	24 mm.	18 mm.

6. *Subject on right side.*

	At beginning.	After 30 minutes.
Right diaphragm excursion	8 mm.	13½ mm.
Left diaphragm excursion	24 mm.	24 mm.

7. *Subject on right side.*

	At beginning.	After 60 minutes.
Right diaphragm excursion	21 mm.	16½ mm.
Left diaphragm excursion	16½ mm.	18 mm.

8. *Subject on right side.*

	At beginning.	After 60 minutes.
Right diaphragm excursion	19½ mm.	16½ mm.
Left diaphragm excursion	11 mm.	22½ mm.

9. *Subject on left side.*

	At beginning.	After 30 minutes.	After 60 minutes.
Left diaphragm excursion	10½ mm.	9 mm.	9 mm.
Right diaphragm excursion	16½ mm.	15 mm.	15 mm.

10. *Subject on left side.*

	At beginning.	After 30 minutes.	After 60 minutes.
Left diaphragm excursion	22½ mm.	21 mm.	21 mm.
Right diaphragm excursion	19½ mm.	19½ mm.	21 mm.

11. *Subject on left side.*

	At beginning.	After 55 minutes.
Left diaphragm excursion	18 mm.	18 mm.
Right diaphragm excursion	22½ mm.	18 mm.

12. *Subject on left side.*

	At beginning.	After 30 minutes.	After 60 minutes.
Left diaphragm excursion	21 mm.	16½ mm.	15 mm.
Right diaphragm excursion	22½ mm.	18 mm.	16½ mm.

Adams and Pillsbury concluded that breath, voice and whisper sounds and tactile fremitus were all increased in the dependent lung as compared with the opposite side.

The following notes were made regarding respiratory sounds:

1. Subject on left side.
   At the end of one hour the vesicular murmur was decidedly more distinct at the front and the back of right apex.
2. Subject on left side.
   At the beginning breath sounds were more audible and distinct over right upper portion of chest. At the end of one hour breathing very quiet on both sides.
3. Subject on left side.
   At the beginning and after fifty-five minutes the vesicular murmur most distinct over front of right apex. Breathing at both bases very quiet.
4. Subject on left side.
   Breath sounds at the beginning and at end of an hour more audible front and back over right apex.
5. Subject on right side.
   At the beginning the vesicular murmur is more distinct at back of left apex than on right. Breath sounds in front about equal. Breathing at bases front and back very quiet. After one hour the vesicular murmur is still more distinctly audible at the back of left apex. No difference noted in front. Breathing at bases front and back very quiet.
6. Subject on right side.
   After one hour vesicular murmur most distinct at back of left apex. In front the breath sounds are equal in intensity. Breathing at bases very quiet front and back.
7. Subject on right side.
   After five minutes it was noted that the breathing at the front of right apex decreased in intensity when compared with same area of left lung. No difference noted in breath sounds at bases.

8. Subject on right side.

At the beginning the breath sounds at the right base were a little more audible than those at left base. Breathing at the apices the same on both sides. The intensity of breath sounds at the front of the right apex less distinct than over the same area on left side.

9. Subject on right side.

After thirty minutes the breathing on both sides was quiet, the right side being generally the quieter.

10. Subject on right side.

After lying in this position for thirty minutes, breath sounds in front over right apex are a little quieter than over left apex. In the lower parts of chest there is no change. At the back to the third dorsal spine the breath sounds are equal in intensity on the two sides. Below this the breath sounds on the recumbent side are more audible.

11. Subject on right side.

The diaphragm at the beginning shows greater excursion on the right than on the left, therefore the breath sounds at the base are intensified on the right. Very little change is noted at the apices. At the end of fifteen minutes diaphragm of dependent lung still shows greater excursion and breath sounds at the right base are still more audible than at the left base. At the apex in front the sounds are more audible on left side. At the end of thirty minutes the breath sounds were much more quiet at the right apex than at left. Otherwise the breath sounds were very quiet throughout both sides.

12. Subject on right side.

At the beginning breath sounds at right base anteriorly more audible than at left. Breath sounds more audible at left apex than at right apex. At the end of an hour breath sounds were more audible front and back at left apex.

13. Subject on right side.

    The subject was noted as breathing more decidedly with diaphragm than the other subjects. At the beginning scarcely any breath sounds can be heard at the right apex. At this time the vesicular murmur was heard more markedly on the right side opposite the eighth dorsal spine. The breath sounds in front were a little more audible on the left side.

14. Subject on right side.

    The breath sounds are very faint over both sides but less audible over recumbent side. The percussion note is hyperresonant over left side, especially over lower part of chest. The vocal fremitus definitely increased over dependent side, more decided in front.

Conclusions.

1. In all the subjects studied the heart and mediastinum become displaced toward the chest wall of the dependent side.
2. In most subjects—but not in all—the diaphragm on the dependent side at first increases its excursion. In all cases this diaphragm, forced up by the abdominal viscera, holds a relatively higher position than that of the upper half.
3. The preliminary increase of diaphragm excusion on the dependent side is associated with an increase in the vesicular murmur at the base on that side.
4. At the end of from thirty to sixty minutes the increase in diaphragm excursion and intensity of basal breath sounds have subsided. The diaphragm movement of the two sides may be equal or reversed.
5. In general the breath sounds at the apex are less audible on the recumbent side.

DISCUSSION

Dr. F. T. Lord, Boston: As I understand Dr. Webb, he ascribes the cardiac displacement in these cases to the pushing up of the diaphragm by the abdominal contents. If this were the explanation the heart would tend to be displaced to the opposite rather than toward the affected side. Is not some degree of atelectasis of the dependent lung a more likely explanation of the cardiac displacement?

Dr. G. B. Webb (closing): I think there is atelectasis on the dependent lung, but the rays do not penetrate clearly. It is very difficult to see through the dependent lung with the fluoroscope. With a deep inspiration the lower part of the lung illuminates very well. There may be a movement of the heart to the other side, but the heart drops over as the effect of gravity and atelectasis on that side.

THE HEMOLYTO-POIETIC SYSTEM IN THE PRIMARY ANEMIAS, WITH A FURTHER NOTE ON THE VALUE OF SPLENECTOMY[1,2]

By E. B. KRUMBHAAR, M.D., Ph.D.
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It is convenient and desirable, from a practical point of view, to consider all diseases of the blood, but especially the so-called "primary anemias," from the dynamic standpoint of the constant interplay of the blood-forming and blood-destroying apparatus (which may be termed the hemolyto-poietic system and the adjustment thereof spoken of as the hemolyto-poietic balance). By using the various diagnostic measures now available there can thus be determined not only the actual disease in question, but whether it is chiefly due to an excess of blood destruction or to a paucity of blood formation; and in the individual case, how grave a disturbance of this hemolyto-poietic balance exists and whether it is becoming more or less upset.

Hemolyto-poietic Balance. A correct estimation of the condition of this mechanism at a given moment (practically the hemato-poietic-hemolytic index of Schneider[3]) is rendered difficult, both by the semiquantitative nature of some of the tests required and by the complexity of the system itself. To discuss the latter point first, a steadily accumulating mass of evidence is forcing us to recognize that bone marrow, lymph nodes, spleen, liver and

[1] The "hemopoietic system," as it has been loosely designated, is not a desirable term, as it ignores the blood-destroying mechanism, which is at least of equal importance with that of blood formation. Custom has long sanctioned the use of "hemo" rather than "hemato," in the compound word.

[2] From the Laboratories of the Philadelphia General Hospital.

[3] Schneider, J. P.: Journal Lancet, 1917, xxxvii, 105; Arch. Int. Med., 1916, xvii, 32; Ibid., 1917, xix, 156.

the whole "reticulo-endothelial apparatus"[4] must be considered as definite a mechanism for the control of the cellular elements of the blood as the digestive or endocrine systems are in their respective spheres. As with the latter system, the complexity of the problem is made more acute by the marked (and as yet imperfectly delimited) ability of one member of the system to take over, in times of stress, functions belonging primarily to some other member of the group. Thus, where blood destruction is greatly increased (as in hemosiderosis, some cases of pernicious anemia and chronic malaria) or in experimental plethora,[5] or after the administration of hemolytic immune serum,[6] the products of blood destruction are found in Kupffer cells, lymph nodes and bone marrow (parts that ordinarily are not noticeably concerned in this process) in much larger quantities than in other parts of the body. The quick response of the normal bone marrow to demands for more blood cells is well known, but, in addition, if sufficiently intense and protracted strain is put upon the blood-forming apparatus, it is not infrequent to find other members of the hemolyto-poietic system reverting to their embryonal functions or metaplastically taking on myeloid activity;[7] and even in a case I recently reported, the bone-marrow assumed definite lymphopoiesis.[8] By quite similar reasoning is to be explained the adjustment that follows splenectomy in normal individuals, whereby after a relatively short period of time the splenectomized patient or animal returns practically to normal in most or all hematological details.

[4] By "reticulo-endothelial apparatus" is meant the widespread cells of reticular or endothelial origin that possess marked capacity for phagocytosis of foreign bodies, body cells, bacteria, etc. They are similar to or identical with the macrophages of Metchnikoff, klasmatocytes of Ranvier, adventitia cells of Marchand, resting wandering cells of Maximow, pyrrhol cells of Goldmann, endothelial leukocytes of Mallory, histiocytes of Aschoff. Jaffé (Wien. klin. Wchnschr., 1922, xxxv, 595) has shown that they are functionally significant as the Kupffer cells of the liver, the pulp cells (splenocytes) of the spleen and the endothelium of spleen, lymph nodes, bone marrow and adrenal and reticulum of spleen, lymph nodes and bone marrow.

[5] Krumbhaar, E. B., and Chanutin, A.: Jour. Exp. Med., 1922, xxxv, 847.

[6] Pearce, R. M., Krumbhaar, E. B., Frazier, C. H.: The Spleen and Anemia, Lippincott, 1917, p. 180.

[7] Donhauser, J. L.: Bull. Ayer Clin. Lab., 1908, v, 46. Bunting, C. H.: Jour. Exper Med., 1906, vii, 365. Dominici: Arch. de méd. expér. et d'anat. path., 1901, xiii, 1. Domarus: Arch. exp. Path. u. Phar., 1908, lviii, 319. Tanaka: Ziegler's Beitr., 1912, liii, 388 (Lit).

[8] Krumbhaar, E. B.: Jour. Med. Research, 1922, xliii, 369.

Methods Available. Reverting to what I have spoken of as the semiquantitative nature of some of the tests involved, I would like to review what evidence may be obtained toward estimating the amount of blood-cell formation and destruction. Although this involves statements that are far from new, I hope that the repetition will be pardoned, in view of the fact that apparently in few clinical laboratories or in few reported cases in the literature has full advantage been taken of available methods.

On the side of blood destruction is the evidence to be obtained from the appearance of the erythrocytes when vitally stained or in stained spreads, and, more directly, from the urobilin output in feces or duodenal contents. According to current views,[9] erythrocyte destruction begins while the cells are still in the circulation. By a process of fragmentation they become smaller and smaller until the disintegrated products are taken up as hemoglobin-bearing dust chiefly by the spleen, to be turned over to the liver by steps that we know little about, there to be excreted as bile pigment with conservation of the iron moiety. Microcytes, therefore, in the peripheral blood, and poikilocytes as well, are to be taken as evidence of increased blood destruction. This has clinical confirmation in hemolytic jaundice—the disease *par excellence* of excessive blood destruction, where microcytes are notoriously numerous. However, Price-Jones[10] has recently showed that whereas in pernicious anemia the average size of the red cell is greater than normal, after hemorrhage it is smaller than normal—a sign, therefore, of deficient blood formation. The degenerated "stippled" erythrocytes of lead poisoning are not within the scope of this paper.

The urobilin output should give us direct evidence of the amount of blood destruction, but unfortunately hitherto unsurmountable difficulties leave this still as a semiquantitative test only. If the original technic of Wilbur and Addis[11] is followed, not only is the test a fairly lengthy one, but the unknown factor of the amount of urobilin absorbed by the intestine cannot be accounted for. In Schneider's method of using a sample of duodenal juice, nor-

[9] Rous, P., and Robertson, O. H.: Jour. Exper. Med., 1917, xxv, 651 and 665.
[10] Price-Jones, C.: Jour. Path. and Bacteriol., October, 1922, xxv, 487.
[11] Wilbur, R. S., and Addis, T.: Arch. Int. Med., 1914, xiii, 235. [12] Loc. cit.

mal fluctuations of output, as well as obvious difficulties in collecting a valid sample, present to my mind even greater handicaps. In addition, there has been no standardization of several factors such as intensity of light, width of column of fluid and other details which may seriously affect the reported result; and in Todd's book on *Clinical Diagnosis* (1919), and Haden's on *Clinical Laboratory Methods* (1923), the only text-books I can find in which the test is mentioned at all, calculations apparently give a result ten times greater than Wilbur and Addis intended. This state of affairs is so regrettable that work is now going on in our laboratories to make this test more serviceable by eliminating preventable errors. Fortunately, the different results obtained in hyperhemolysis or hypopoiesis (as compared with the normal) are so great that, in spite of the difficulties first referred to, I am confident the test will prove to be of sufficient value to be used in every carefully studied case of anemia.

On the side of blood formation, information can be obtained from the blood counts (hemoglobin, erythrocytes, leukocytes, platelets), especially if frequently repeated accounts are made; but care should be taken not to place reliance on variations so slight that they are within the limits of observational error. The less constant the conditions attending the various tests and the less your acquaintance with the source of the report the greater should be your conservatism in this respect. Especially valuable information may be obtained from a properly prepared vital or stained spread. Nucleated forms are a sure indication of bone-marrow activity, and quantitative comparisons may, therefore, be used to estimate roughly both the stress of the demand and the ability to supply. The normoblast may appear in any severe anemia; the megaloblast, or earlier form, is more rarely found, except in pernicious anemia, where it possesses diagnostic value. Nuclear remnants, Heinz bodies, Howell-Jolly bodies and Cabot rings are similar signs of bone-marrow activity. In terminal conditions, however, many and bizarre nucleated forms may appear in the blood stream without finding any bone-marrow hyperplasia at autopsy. The size and shape of the erythrocytes have been already referred to; numerous macrocytes, presumably com-

ing from megaloblasts, suggest pernicious anemia. Extensive polychromatophilia (young erythrocytes) also indicates bone-marrow activity, though this is better brought out by the special search for reticulocytes in "vital spreads."[13] Like the urobilin test, this simple test deserves much more frequent use than has yet been accorded it. It is not only a sensitive method of ascertaining and following the bone-marrow activity in a given case, but in hemolytic jaundice, where for some unexplained reason there is a marked reticulosis, it assumes diagnostic value. The shower of nucleated forms and increased number of reticulocytes and platelets in pernicious anemia following splenectomy and at the beginning of a remission are both well-known phenomena.

Finally, the test for the resistance of erythrocytes to hypotonic salt solution[14] determines this phase of blood-cell formation and indirectly throws light on the diagnosis and severity of the process. In hemolytic jaundice, essentially a disturbance in the resistance of the erythrocytes, this test is pathognomonic.

Results of Treatment. Treatment of any anemia is naturally directed toward relieving the anemia and removing the cause. The best methods of securing the former of these factors cannot be discussed here, while the attainment of the latter is obviously apparent in secondary anemias. It is in the so-called "primary anemias," however, where the causes are unknown, that the most earnest attempts have been made to restore the lost hemolytopoietic balance by direct intervention with one or other member of the system. Removal of the spleen, one of the chief agents of blood destruction, has proved valuable to a greater or less degree in the several diseases of this group, the value of the procedure always being due to removing one of the chief agents of blood destruction. Although, as is shown in the diagram I have presented, this function can be and is taken over by other members of the hemolytopoietic system it is not exerted to such a great extent for a considerable period, and in some case not ever. According to the doctrine of "hypersplenism," the diseased spleen

[13] Vogel, C.: Arch. Int. Med., 1913, xii, 707. Krumbhaar, E. B.: Jour. Lab. and Clin. Med., 1922, lxxix, 1879, etc.

[14] Pearce, R. M., Krumbhaar, E. B., and Frazier, C. H.: The Spleen and Anemia.

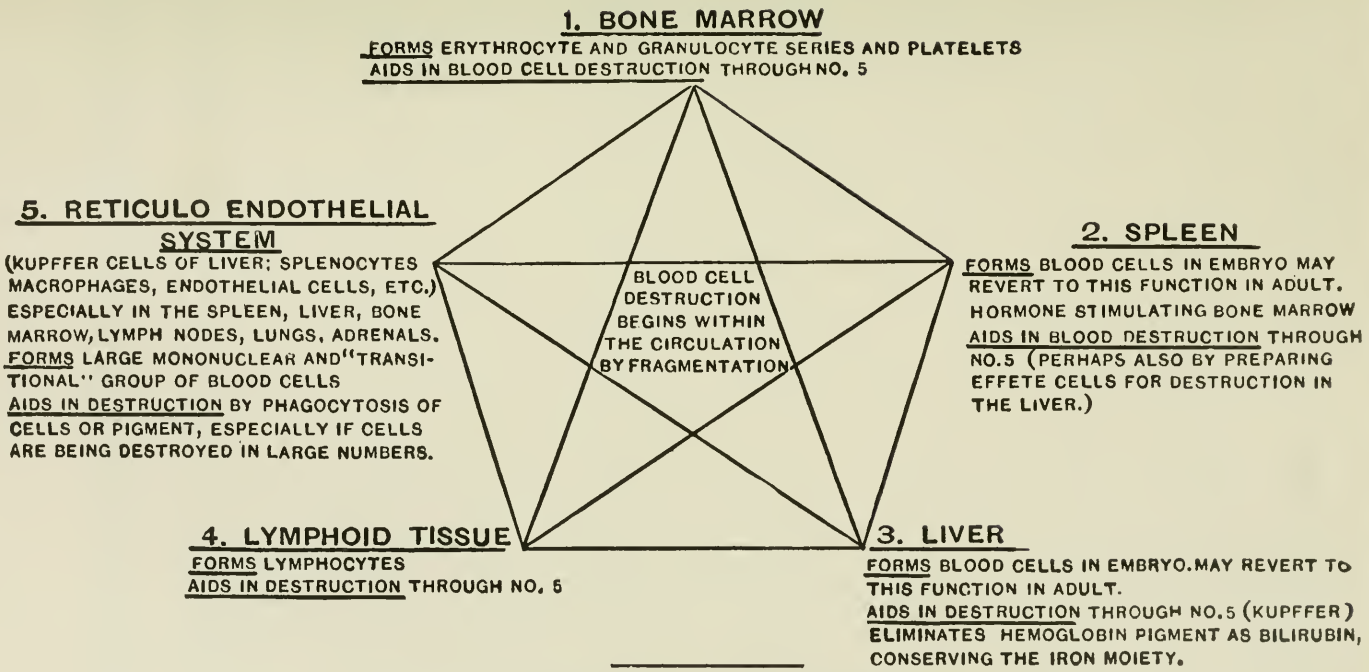
1. BONE MARROW
FORMS ERYTHROCYTE AND GRANULOCYTE SERIES AND PLATELETS
AIDS IN BLOOD CELL DESTRUCTION THROUGH NO. 5
2. SPLEEN
FORMS BLOOD CELLS IN EMBRYO MAY REVERT TO THIS FUNCTION IN ADULT.
HORMONE STIMULATING BONE MARROW
AIDS IN BLOOD DESTRUCTION THROUGH NO.5 (PERHAPS ALSO BY PREPARING EFFETE CELLS FOR DESTRUCTION IN THE LIVER.)
3. LIVER
FORMS BLOOD CELLS IN EMBRYO. MAY REVERT TO THIS FUNCTION IN ADULT.
AIDS IN DESTRUCTION THROUGH NO.5 (KUPFFER)
ELIMINATES HEMOGLOBIN PIGMENT AS BILIRUBIN, CONSERVING THE IRON MOIETY.
4. LYMPHOID TISSUE
FORMS LYMPHOCYTES
AIDS IN DESTRUCTION THROUGH NO. 5
5. RETICULO ENDOTHELIAL SYSTEM
(KUPFFER CELLS OF LIVER; SPLENOCYTES MACROPHAGES, ENDOTHELIAL CELLS, ETC.) ESPECIALLY IN THE SPLEEN, LIVER, BONE MARROW, LYMPH NODES, LUNGS, ADRENALS.
FORMS LARGE MONONUCLEAR AND "TRANSITIONAL" GROUP OF BLOOD CELLS
AIDS IN DESTRUCTION BY PHAGOCYTOSIS OF CELLS OR PIGMENT, ESPECIALLY IF CELLS ARE BEING DESTROYED IN LARGE NUMBERS.
BLOOD CELL DESTRUCTION BEGINS WITHIN THE CIRCULATION BY FRAGMENTATION

FIG. 1. HEMOLYTO-POIETIC SYSTEM

has developed this function to a pernicious extent, a condition which may not be attained by the other members of the system after splenectomy.

In considering in a more detailed manner the effects of splenectomy in individual diseases, the condition has not materially changed since I last collected reports on this question.[15] [16] Nevertheless, by a swing of the pendulum, which is so common in medical advance, splenectomy for pernicious anemia, the most important disease of the group, is now, in my opinion, being neglected just as much as it was being overdone six years ago. The conclusions that were reached at that time have, it seems to me, largely been confirmed by subsequent studies. The operative mortality has been lowered, and most of the survivors have shown marked temporary improvement, the remission usually lasting longer than the average length of natural or post-transfusional remissions. In fact, there is a respectable number of cases that have continued in good health for two to six years after splenectomy. Therefore, my former question, "May it not develop that a larger percentage of such cures (3 in 1200 by the older methods, according to Cabot) will follow splenectomy even though the blood picture does not return absolutely to normal?" can, I think, properly be answered in the affirmative. Of the 196 cases in my list, Giffin reports that 11 of his 53 lived more than three years after operation and 5 still live between four and five years after operation. Of Walterhofer's 16 cases, 1 survived for five years, and 2 more for from two to four years, and so on. This does not mean that every case of pernicious anemia should have the spleen removed or that a cure should ever be hoped for; but it does, to my mind, indicate that in certain cases, especially those that have a relatively recent onset, with a fair blood picture, signs of an enlarged spleen and increased hemolysis, splenectomy is usually advisable. How it should be combined with transfusions is a question that I cannot take up at this time.

In hemolytic jaundice the results of splenectomy continue to be excellent. Although in many cases the resistance of the erythro-

[15] Krumbhaar, E. B.: Trans. Coll. Phys., Philadelphia, 1916, xxxviii, 35, 158.
[16] Krumbhaar, E. B.: Pernicious Anemia, Jour. Am. Med. Assn., 1916, lxvii 723.

cytes does not return to normal (indicating that the primary cause of the disease is not in the spleen but probably in the erythrocytes themselves), nevertheless the anemia and jaundice disappear, the urobilin excretion and reticulocyte percentage diminish and the patient is for practical purposes well. If Mayo's caution not to operate during a "crisis of deglobulization" is heeded, the operative mortality may be reduced even below the present rate of 3 per cent.

The improvement that has long been known to follow splenectomy in Banti's disease is supported by the later figures. Abdominal adhesions and hemorrhage from varicose veins add to the difficulties of the operation, but marked improvement can be promised to most of the survivors. In fact, many have continued so long without symptoms that they have been reported as cured, but it is unwise to use the term "cure," when the operative procedure has merely removed the chief disturber of the hemolytopoietic balance rather than the cause of the disease itself. It is of course, recognized that as negative methods are the only ones at present available for diagnosing Banti's disease, many cases of splenomegaly due to lues, cirrhosis, portal phlebitis and similar causes are undoubtedly included, and it is especially hard to distinguish them when successful removal of the spleen in the latter group also results in improvement. Nevertheless, the conviction persists that Banti described a primary disease the cause of which is unknown, but which is greatly improved by removal of the spleen.

The most important additions that have been made to our knowledge of this subject in recent years have come from the Mayo Clinic.[17] [18] Thanks to them not only have most of our previous opinions been confirmed, but reliable estimates made about the value of splenectomy in newer fields. Thus while leukemia used to be considered as definitely contraindicated on account of the high operative mortality (see Table I), the Mayos have had only 1 postoperative death in 26 cases (much less than in splenic anemia); on the other hand, 15 have subsequently died, so that Giffin considers splenectomy helpful only in a few of the very

[17] Mayo, W. J.: Jour. Am. Med. Assn., 1921, lxxvii, 34.
[18] Giffin, H. Z.: Minnesota Med., 1921, iv, 132.

chronic types of myelogenous leukemia where the organ is fibrous and the leukocyte count never very high. Splenectomy in cases of splenomegaly associated with chronic sepsis has also proved unsatisfactory, both on account of the high operative mortality (20 per cent) and the poor end-result (3 out of 10 survive, and 1 of these is in poor condition). In luetic and malarial splenomegaly not only are the patients' conditions directly improved by removal of the spleen, but they are also usually rendered much more amenable to specific treatment, to which they may previously have proved intractable. In fact, if I may venture an opinion on what is more directly a surgical problem in such secondary splenomegalies, the question being mainly one of operative risk, it would seem desirable to limit the operation to chronic cases that have proved resistant to all other forms of treatment and to proceed with extra conservatism where many adhesions multiply the chances of shock and hemorrhage.

TABLE I. RESULTS OF SPLENECTOMY IN MEDICAL DISEASES.*

Disease.	Number of cases.	Postoperative death (within 1 month).	Postoperative mortality. Per cent.	Record of subsequent death.	Unimproved.	Improved.	Apparently cured.
Splenic anemia	293	40	13.6	24	4	178	35
Gaucher's disease	16	4	25.0	1	..	9	1
v. Jaksch's disease	19	..	..	1	..	11	1
Hemolytic jaundice	137	4	2.9	..	..	5	125
Pernicious anemia	208	35	16.8	79	26	146	..
Myelogenous leukemia†	80	47	58.7	21	2	7	..
Liver cirrhosis	19	6	31.6	5	4	7	..
Luetic splenomegaly	7	1	14.3	..	..	6	..
Tuberculous splenomegaly	17	2	11.7	2	1	11	..
Malarial splenomegaly	250	48	19.2	..	..	202	..
Hemorrhagic diathesis	27	2	7.4	..	1	9	15
Total	1073	190	17.6	133	38	591	177

* The postoperative mortality in recent reports of this disease is no higher than the average of other diseases of the list.

† Although larger than any figures heretofore published on this topic, this table by no means attempts to be a complete list. It has been compiled from reports from the following authors:

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Summary. 1. Bone marrow, spleen, liver, lymph nodes and reticulo-endothelial apparatus combine to regulate the formation and destruction of blood cells in what may be termed the "hemolyto-poietic system."

2. The methods for studying the functioning of this system ("hemolyto-poietic balance") are discussed.

3. The results of splenectomy in various diseases affecting this balance are presented.

DISCUSSION

Dr. A. S. Warthin, Ann Arbor, Mich.: The reticular endothelial cells of the hematopoietic system have a scavenger function and will take up anything in the blood or lymph stream. The Kupfer cells of the liver have been found loaded with broken-down lymphocytes in cases of lymphosarcoma and leukemia treated by irradiation. That the reticuloendothelial cells of the hemolymph nodes and glands of the spleen take up blood pigment and malaria is well known. I think that their function in general is a protective one and that the role of scavenger of blood pigment is only one manifestation of their protective activity. It is misleading to ascribe the greatest prominence to this phenomenon which is only one of their functions.

Dr. G. B. Webb, Denver, Col.: In regard to the marrow-producing lymph elements, many years ago it was noted that at high altitudes lymphocytosis was increased on account of the hyperplasia of the marrow. Hyperemia would bring up the same result. Even the practice of putting on garters would cause an enormous lymphocytosis—about 80 per cent. We were never able to describe these cells. Ehrlich hesitated to give a name to them; they appeared like transitional cells. It is interesting to know that the bone marrow takes part in the lymphoid elements.

Dr. E. B. Krumbhaar (closing): I quite agree with Dr. Warthin that the cells of the reticuloendothelial apparatus have a broader function than merely that of aiding in hemolysis. I think that that statement applies also to the Kupfer cells. Lepehne, in an experiment reported several years ago, using collargol-saturated dogs, showed that the animals failed to become jaundiced like the controls, after the injection of hemolytic agents, because the Kupfer cells were already stuffed with collargol and so could not act on the destroyed blood cells. There are, of course, many functions of the hemolytopoietic system that are not yet clearly comprehended, but I hope by this general introduction to promote recognition that such a system does exist and to stimulate interest in clearing up some of its obscure relations.

ABSCESS OF THE LUNG

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Introduction. This report is based upon our experience with 60 cases, mostly seen in the last two years. The comparatively large number of cases observed during so brief a period appear to indicate that abscess of the lung is a more common condition than is generally appreciated.

A study of the literature indicates the existence of considerable confusion in the reports on various suppurative lung conditions. There would appear to be need for greater accuracy in definition between acute pulmonary abscess, chronic pulmonary abscess, so-called gangrenous abscess and pulmonary gangrene and bronchiectatic abscess and bronchiectases.

The differential diagnosis is not always easy, as our best means of arriving at this is the *x*-ray and the pictures presented by acute abscesses and acute exacerbations engrafted on chronic underlying lesions may be quite similar. The histories in many cases may lead us to suspect the existence of a chronic etiological factor, but often it may be impossible to obtain the facts, and yet the importance of making this distinction is obvious, as proper treatment depends largely upon its accuracy.

The series here reported has to deal mainly with acute pulmonary abscess, 46 of the 60 cases being of that nature.

Etiology. It is generally considered that pulmonary abscess follows a pneumonia in which necrosis and liquefaction supervene. It is usually considered a primary broncho and lobar pneumonia or one secondary to other conditions such as operations on the

upper air passages, aspiration of foreign material, traumatism to the chest and pyemic metastases from suppurating foci elsewhere in the body.

Our experience leads us to surmise that the condition of abscess of the lung may occur without any evidence of preceding pneumonia. Such a condition may be supposed to be an abscess primarily from the start, the interstitial tissue of the alveoli being infected and the inflammatory products breaking down promptly without any definite stage of an exudative pneumonia into the air vesicles.

In our series such primary abscesses would appear from the history to have been a probability in 22 of the 60 cases.

The history of such cases is a rather short and not very acute prodromal period which develops in a short time, usually within a week, into the definite symptoms of an abscess discharging into a bronchus, evidenced by the expectoration of considerable quantities of pus.

In favor of such an hypothesis of primary abscess formation is the fact that secondary abscesses in the same or opposite lung not infrequently occur. That these secondary abscesses have the same character as the original lesion, without signs or symptoms of a preceding pneumonia, and following the inhalation of foreign bodies such abscesses are well recognized, independent of any intermediate pneumonic stage.

This primary abscess formation may occur either because of local favoring factors in the lung itself or because of the nature of the infecting agent.

Among these local factors in the lung itself the irritant action of ether vapor should be considered as one. The incidence of postoperative pneumonia following its inhalation and its deleterious effects on those suffering from preëxisting pulmonary lesions but confirm this view. As to the nature of the infecting agent, our observations upon the bacteriology may have a bearing upon this question.

The usually accepted idea of the bacteriology of lung abscess is that of a very mixed group of pyogenic organisms upon which may be engrafted the putrefactive organisms in the case in which gangrene appears.

Our studies of the bacteriology are limited to only 10 of our cases in which the examinations were made directly from the abscesses at the time of operation. They do not include any studies of the sputum, for these are unreliable on account of the ready liability to contamination with bacteria from some other portion of the respiratory tract.

The striking results of these bacterial examinations of the abscess pus in these 10 cases were the uniform presence of anaërobic bacteria which were present in predominating numbers in all and were the only type of organism found in 8 of the 10 cases.

In the other 2 cases streptococci were found, one a hemolytic and the other a non-hemolytic variety, in addition to the anaërobic bacteria.

The anaërobic flora found were quite variable, being a streptothrix in 6 cases, a Gram-positive coccus in 6, a Gram-positive bacillus in 4, a Gram-negative bacillus in 7, a fusiform bacillus in 2, and a spirillum closely resembling that in Vincent's angina in 1 case.

It was interesting to note that in 1 of our cases successfully operated upon for abscess in the right lower lobe, 2 anaërobic organisms, a streptothrix and a Gram-negative bacillus were the only bacteria found, and that sixteen months later, after the patient had become apparently well, another pulmonary abscess developed in the right upper lobe, and from which the identical two organisms were again the only ones isolated from this abscess at the second operation.

We have attempted some preliminary experiments with monkeys in the endeavor to produce lung lesions by intratracheal injection of these anaërobic organisms, and in one monkey this was done in conjunction with tonsillectomy. The animals reacted with some fever for a few days, but no lung lesions were produced.

We shall continue this study as it appears to us to have an important bearing on the subject.

The fact that some of these anaërobes correspond to the type found in the mouth and throat in such conditions as pyorrhea and Vincent's angina raise the further interesting query whether the well-recognized relationship between pulmonary abscess and

operations upon the upper-air passages may not, in part at least, be due to the pathogenic possibilities of these anaërobic bacteria in producing abscess when they reach the lung under the varying conditions of the inspiration of foreign infected material at the time of such operation.

Methods of Treatment

The cases of this series, with 4 exceptions, have been studied jointly from the medical and surgical points of view, the hospital cases which compose the larger part being the subject of a medico-surgical conference held at least once a week during the entire period of their observation. This we believe is the ideal method of investigation.

Originally we approached the problem of their treatment as primarily a surgical one and in the earlier part of our studies we were inclined to advocate early operation as soon as the diagnosis was accurately established. These operations were performed independent of the age of the patient, his condition or the type of lesion present. The results were most disheartening and consequently about one year ago we radically changed our procedure by treating them primarily as medical cases, advocating operation only after medical treatment had failed or after the local conditions for successful operation had become more favorable.

The medical treatment consisted of rest and postural drainage, the latter carried out regularly four or five times a day for periods varying from five to twenty minutes each.

Postural drainage is carried out by inverting the patient over the side of the bed with the head down at the floor. This position is maintained for three to five minutes at first and repeated four or five times a day. As the patients become accustomed to it the maintenance of this posture is increased in duration to as long as may be necessary to thoroughly empty the abscess cavity. This is usually not more than fifteen or twenty minutes at each session and is frequently less. The patient soon comes to recognize the period desirable in his individual case and also can appreciate the need for the repetition of the procedure by the returning tendency

to cough and expectorate. When successful this method affords several hours of almost complete freedom from cough and expectoration, is accompanied by marked diminution in the constitutional symptoms and after a few days by a gradual diminution of the total quantity of the expectoration as well as of its fetid purulent character.

We believe that by this method it is possible to increase very materially the number of cases which may be cured by spontaneous drainage through a bronchus. It also will aid in diminishing the extent of the area of inflammatory reaction in the lung surrounding the abscess and also improve the general condition of the patient and render the case more suitable for operation should this become necessary.

The surgical treatment consisted in the main of incision and drainage in one stage if the pleural cavity was walled off by adhesions, otherwise in two stages. Local anesthesia is certainly safer than general anesthesia even with nitrous oxide gas and oxygen. Soft rubber dam we believe the best form of drain, and have abandoned the use of gauze, employing it only to control hemorrhage. We found this operation extremely dangerous and usually unsuccessful in the more acute phases of the disease, that is during that period when there was present about the softened central suppurating focus a more or less extensive zone of edematous, soggy-infected lung in which the smaller bronchi are filled with pus and the alveoli are distended with seropurulent exudate and while the walls of the alveoli are swollen and edematous. None of these cases were seen prior to their rupture and communication with a bronchus.

Our experience has led us to believe that incision of the abscess at this time fails to effectively drain the entire infected area and that with a free opening established the effectiveness of coughing in emptying these areas is greatly reduced. In many of our cases opened during this stage there was a pronounced improvement for a few days, the expectoration was diminished, the temperature became normal and the patient apparently was making a satisfactory recovery. But this period was followed by a wide extension of the pneumonic process, sometimes ushered in by a chill and a

fatal termination in from three to five days or a week. At autopsy there was found a widespread, massive involvement of the entire lung or both lungs, in which the bronchi were filled with pus and the alveoli either showed the changes of an acute pneumonia or with alveoli swollen and edematous and infiltrated with leucocytes. In some cases which lived long enough there were multiple small abscesses widely disseminated throughout the lungs.

After postural drainage, however, even if it does not effect a cure in itself, there is usually a definite improvement in the constitutional symptoms and a clearing of this secondary zone of infiltration about the abscess, which renders an operation much more liable to succeed.

There is a period in lung suppuration when the alveoli in the immediate vicinity of the abscess are collapsed but with the respiratory epithelium still intact, and when they are therefore capable of reaeration, and this is the most favorable time in which to operate.

If, however, the suppuration continues this epithelium disappears and the alveoli become obliterated and there is found a true connective-tissue layer composed of the fused alveolar walls observed in chronic abscesses, a condition most unfavorable for a complete cure and one which favors the establishment of a permanent bronchial fistula.

The problem is to give each patient a full chance to reach this more favorable stage and at the same time not to allow the disease either to extend indefinitely or to drift into the chronic abscess with thick fibrous wall, which is unfavorable for radical cure by operation or any other method of treatment.

This can only be done by the close coöperation of physician and surgeon in the study of the case, and particularly the comparison of frequent *x*-ray plates of the chest.

From three to four weeks of such medical treatment may usually safely be employed to determine the necessity for operation, in which time many will recover without it.

More radical operation in the form of lobectomy, although successful in 1 of the 3 cases in which it was attempted in this series, must still be considered as an extremely hazardous procedure, although theoretically it might be considered the ideal treatment

when by an improvement in surgical technic it is possible to diminish the present great operative risk. The successful case was one seen by Dr. Miller. The lobectomy was performed by Dr. Lilienthal, who obtained a truly brilliant result.

Artificial pneumothorax is being quite extensively advocated for the treatment of acute pulmonary abscess. Our experience has been very limited, it being used only in the case of 7 patients, none of whom improved and 2 of whom died.

We do not wish, however, to have this considered as our final judgment upon this method of treatment, for it seems quite possible that it may be of help in acute abscesses freely opening into a bronchus and situated near the hilum of the lung.

We do wish to emphasize, however, that its use in peripheral abscesses is attended with great danger of rupture of the lung with subsequent pyopneumothorax, and this actually happened in 2 of our cases and has been quite frequently reported in the literature. Also, it is our experience that this method of treatment may do harm in the case of abscesses not situated near the hilum by exerting pressure on the proximal portion of the bronchus and thus shutting off drainage, and it also may inhibit drainage by preventing the normal expulsive power of coughing. In 1 case we employed this method very successfully for the control of large and repeated hemorrhage.

Bronchoscopic Lavage. Bronchoscopical suction and lavage has also been very favorably advocated in the treatment of pulmonary abscess. Our experience has been limited to 3 cases, which were referred to the laryngoscopical division of the hospital for this treatment. Of these 3 cases, 1 was improved, 1 not improved and 1 died, apparently from a rupture of the lung directly following the treatment. We have no desire to record a final judgment upon this method from our scant experience, and bronchoscopical examination is highly to be recommended in cases of suspected foreign body in the lung and for the diagnosis.

We are, however, rather deeply impressed with the fact that this procedure is a very trying ordeal for acutely ill patients, and also we are not convinced that it is unattended by a real risk to the patient.

Analysis of Cases. *Sex.* Forty-five cases were in men and 15 in women, a proportion of 3 to 1 in favor of men. This is in accord with the reports of other observers.

Etiology. The cause of pulmonary abscess in a given case is not always easy to establish. As far as we could determine from the histories the etiological factors in this series may be grouped as follows:

No definite cause (primary abscess)	22
Secondary to pneumonia	16
Secondary to postoperative pneumonia	3
Secondary to tonsillectomy	8
Secondary to other operations	5
Following tooth extraction	2
Following submersion	2
Following foreign-body inhalation	1
Following trauma to chest	1
	60

The high incidence of cases (36.6 per cent of all) to which no definite primary cause may be ascribed is noteworthy. Also the occurrence of abscess following tonsillectomy is lower than in many other series reported.

Duration of Disease. The duration of the disease before coming under observation is important from the standpoint of methods and results of treatment.

Less than 1 month	23
From 1 to 3 months	23
From 3 to 6 months	7
Over 6 months	7

Forty-six of these cases (76.6 per cent) may be therefore considered as acute abscesses.

The results of treatment show that of the 23 cases of less than one month's duration, 14 (60.8 per cent) were cured and 5 died, a mortality of 21.3 per cent.

Of the 23 cases from one to three months' duration 6 (26 per cent) were cured and 9 (39 per cent) died.

Of the 7 cases of three to six months' duration 2 (28.5 per cent) were cured and 3 (42.8 per cent) died.

Of the 7 cases lasting more than six months 3 (42.8 per cent) were cured and 3 (42.8 per cent) died.

The generally recognized predominant importance of early treatment is again emphasized.

Location of the Lesion. The lesions were in the right lung in 40 cases, in the left lung in 19 and in both lungs in 2 cases. They were in the lower lobe in 40 cases, in the upper in 19 cases, in the right middle lobe in 1 case and in both upper and lower lobes in 1 case. Three cases had multiple lobe involvement.

Of the 19 upper lobe cases 10 (52.6 per cent) were cured and 6 (31.5 per cent) died. Of the 40 lower lobe cases 16 (40 per cent) were cured and 12 (30 per cent) died.

These results indicate a somewhat more favorable prognosis in upper lobe cases, but not so marked as some other series have shown.

Results of Treatment. As has already been described, our experience led us to modify our methods of treating these cases very radically.

We are therefore reporting the results in one series as a whole and in addition are reporting separately the comparative results obtained by the two radically different methods. These results are indicated by an early series of 29 cases, in which early radical surgery predominated and second later series of 31 cases in which medical treatment was almost invariably first tried with postural drainage as the most important feature.

Results of Complete Series, 60 cases. Cured, 26; improved, 6; unimproved, 8; died, 20. A mortality of 33.3 per cent.

Results of Early Series, 29 cases. Cured, 11; improved, 2; not improved, 4; died, 12. A mortality of 41.4 per cent.

Results of Later Series, 31 cases. Cured, 14; improved, 5; not improved, 4; died, 8. A mortality of 26 per cent.

The comparison not only shows the later series to much better advantage in increased cures and diminished mortality, but also indicates a larger number who were improved, although not cured, the combined cured and improved cases being 45 per cent in the early series and 61 per cent in the later one. The fact that by medical treatment a certain number of patients were able to go on fairly comfortably without constitutional symptoms and with alleviation of disturbing cough and expectoration influenced not

a few to decline advice to undergo an operation advocated in the hope of effecting a radical cure.

Results Obtained by Various Methods of Treatment. In comparing the two major therapeutic procedures which we have employed in this series, we find that postural drainage was used in 30 cases, of which 14 (46.6 per cent) were cured, 4 (13.3 per cent) were improved, 11 (36.6 per cent) were unimproved and 1 (3.3 per cent) died.

In the operative cases, of which there were 27 in all, 11 (40.7 per cent) were cured, 1 (3.7 per cent) was improved and 15 (55.6 per cent) died.

The very much higher mortality in the operative cases is very striking, although it must be borne in mind that there are here included 8 cases in which medical treatment had first been tried and had failed.

It also must be noted that the operative results in the later series, in which we had arrived at a more satisfactory method of selection of cases as regards the time most suitable for operation, are much more favorable than in the early series. In 14 operative cases of the early series the mortality was 71.5 per cent while in 13 cases of the later series it was only 38.5 per cent.

Summary. 1. Acute pulmonary abscess is a comparatively common and extremely serious disease.

2. Great opportunity for improvement in methods of treatment exists. This can best be met by close combined study of each case by physician and surgeon.

3. It seems probable that many cases are abscesses from the start without going through the intermediate stage of pneumonia.

4. Our studies of the bacteriology would indicate that anaërobic microörganisms may play an important pathogenic role in their causation. Further study of these organisms seems important.

5. The treatment of acute abscess is primarily a medical problem. When surgery is necessary, results are far more successful after preliminary medical observation and treatment.

DISCUSSION

Dr. C. P. Howard, Iowa City: What does Dr. Miller think as to the advisability of aspiration of the chest in a case of suspected lung abscess?

Dr. Thomas McCrae, Philadelphia: I would like to emphasize the value of bronchoscopy and drainage. I have seen a series of cases treated by this method and it has revolutionized my ideas. The results I have seen accomplished are marvelous. Dr. Miller refers to the difficulty of technic. Of course, if the child jumps about on the table it is impossible. When I speak of results, I am not referring to Dr. Jackson but to men trained by him. I think we should all endeavor to carry out bronchoscopy and drainage in our cases as early as we can.

Dr. F. T. Lord, Boston: We have gone through a similar evolution in the treatment of pulmonary abscess with a tendency to give a more thorough trial to medical treatment before the resort to surgery. The immediate surgical mortality is 10 per cent in our abscess cases, and while surgery is indispensable in many cases, yet the risk of operation justifies a postponement of surgery until other means have been thoroughly tried. In the first 100 of our cases there were 7 complete recoveries without resort to surgery, but in later cases the percentage of recovery without surgery has materially increased. This is in part due perhaps to the earlier diagnosis of abscess in a group of relatively mild destructive pulmonary lesions in our later series. I cannot give the exact percentage, but perhaps one-third of our cases of abscess of short previous duration have recovered without operation.

Dr. James Alexander Miller (closing): In regard to aspiration, this we consider an unnecessary and dangerous procedure. We do not recommend it on account of the danger of infection to the pleura, although the pleura is comparatively resistant to infection. As far as bronchoscopy and drainage are concerned, I am prepared to say that perhaps we have not given it a fair trial, but the slight experience we have had has not been very favorable, and in adults it is certainly a trying ordeal for many patients.

A STUDY OF THE PATHOLOGY OF CASES DYING AT CAMP DEVENS DURING THE INFLUENZA EPIDEMIC IN 1918[1]

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AND
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(ABSTRACT)

In this presentation the term "influenza" is used as applying to the pandemic disease which was present in this country during the autumn of 1918. Usage of the term in connection with this disease has been so general that the name "influenza" must continue to apply to this pandemic disease for the present, irrespective of its etiology.

A characterization of this disease influenza is difficult because most of the uncomplicated cases recover, so that the lesions in the various organs cannot be studied. In those cases which die the disease is complicated by the invasion of other microörganisms than the specific cause, so that the lesions due to the disease influenza itself are obscured. Furthermore, the etiology is not determined with certainty.

Of the various agents which have been suggested as causes, Bacillus influenzæ and the Bacillus penumocintes are the most important possibilities at the present time. Although a good deal of evidence may be brought forward to show relationships between these microörganisms and the disease, convincing proof is lacking, and it seems best to consider that the etiology of the disease is unknown.

[1] To appear in full in Archives of Internal Medicine.

This study has consisted in the examination of material from autopsies of cases which died at Camp Devens, Massachusetts, during the epidemic, supplemented by autopsies from the Peter Bent Brigham Hospital, in Boston. The purpose of the study has been the endeavor to identify the lesions which can be attributed to the virus of the disease influenza and thus determine its pathology; also to resolve the various complicated pictures which are found at autopsy which are produced in part by the virus of the disease and in part by the complicating microörganisms. Although the majority of the lesions which are characteristic of this disease have been described by other authors, it is felt that this study has separated out the lesions which apparently belong to the disease influenza from the other lesions commonly present.

The virus of the disease influenza apparently produces certain characterisitic lesions in different organs in the body. Furthermore, the lesions produced by the Bacillus influenzæ following the lesions produced by the virus of the disease influenza form a characteristic picture in the lungs. The lesions elsewhere in the body which occur as a result of the virus of influenza are in some instances peculiar to this virus and in other instances similar to the lesions produced by other agents.

The upper respiratory tract in influenza shows intense congestion with, in some instances, destruction and desquamation of the epithelium and a certain amount of cellular reaction in tissues beneath the epithelium.

In voluntary muscles there is a toxic lesion which causes degeneration up to actual necrosis of the whole or a part of the muscle fiber. In response to the necrosis of the muscle fibers there is a reaction of phagocytic cells and leukocytes and also some reaction on the part of the connective tissue. The partially injured fibers regenerate. This toxic lesion is similar to the necrosis known as Zenker's degeneration of muscle and is met with in various conditions. Secondary invading organisms may reach these necrotic areas in the muscle and produce abscesses.

In the adrenal gland there are necroses of the epithelium of the cortex of the gland and in the cases in which this necrosis is marked there may be a cellular reaction. This lesion in the adrenal is presumably toxic in origin.

In the testicle there is a toxic lesion which causes an injury to the epithelial cells of the tubules, and this is sometimes associated with edema of the interstitial tissue. The cells of the tubules are degenerated and show no evidences of spermatozoa formation. Around the basement membrane of the tubules a hyaline-like substance appears and eventually this substance takes on the appearance of or is replaced by connective tissue. Whether the epithelium of the tubules in the testicles could resume the function of spermatogenesis after this injury was not settled, but no appearance of a restoration of function in many tubules was present in the cases which survived the longest.

The picture in the lung which is due to the virus of the disease influenza is a characteristic one. It consists in the first place of an injury to the epithelium of the lower branches of the bronchial tree and the alveolar walls. The epithelium in addition to becoming necrotic in places desquamates off. There is marked congestion and hemorrhage into the air spaces. The air spaces become markedly dilated and this dilatation of the alveolar spaces goes on to actual rupture in certain instances. In the dilated air spaces and other air spaces there is formed a hyaline-like membrane which is presumably the result of air surrounded by exudate acted upon by pressure. Just what would be the end-result of these lesions in the lung if they remained uncomplicated cannot be determined because the uncomplicated cases did not die. It is probably that healing takes place and the lung returns to normal.

These lesions, which are characteristic of the disease influenza, can be detected in the gross in some cases and under the microscope readily, even in the presence of various inflammatory conditions superimposed in the lung by other organisms. The influenza lesions apparently repair by a regeneration of the epithelium and absorption or organization of the hemorrhage and removal of the hyaline membrane by the action of phagocytes or enzyme action or by organization. Presumably some dilated air spaces return to their normal size.

In the cases in which the influenza lesion in the lung are complicated by the invasion of other organisms such as the pneumococcus and streptococcus, the usual picture produced by the organism is

found superimposed upon the influenza lesions, easily identifiable by the hyaline membranes and acute alveolar emphysema. When, however, the influenza bacillus is the complicating organism a rather characteristic type of bronchopneumonia develops. Extending laterally from the bronchi the inflammatory process goes by direct extension into the surrounding tissues and alveolar spaces. There is considerable cellular reaction and deposit of fibrin with hemorrhage. Vessel walls may be invaded and thrombosis result. The bronchi become dilated, due to weakening of the walls. Destruction of the walls by the inflammatory process and abscess formation are common.

Along with this acute inflammatory process bronchitis and peribronchitis, organization takes place in an attempt to repair and there results a condition in which repair and inflammatory reaction are going on side by side.

The lantern slides which were shown at this stage of the presentation were illustrative of the various lesions seen in the adrenal, testicle and lung.

In conclusion, it may be said that the disease influenza has a definite pathology of its own. It may be recognized even in the presence of lesions produced by various microörganisms. This special pathology is most apparent in the lung, and the most striking pulmonary lesion in the gross is the dilatation of the alveolar spaces with the intense congestion and hemorrhage. Under the microscope, in addition to these lesions, there is the characteristic hyaline membrane. Furthermore, the disease influenza when complicated with the influenza bacillus produces a characteristic type of bronchitis, bronchopneumonia and peribronchitis, with the formation of bronchiectatic cavities in the lung. These lesions can also be readily recognized in the gross inspection of the lungs and on microscopic study.

DISCUSSION

Dr. W. G. MacCallum, Baltimore: I am glad to find that my own report of the lesions in epidemic influenza, given before this society in 1919, is so precisely confirmed in all details. The pictures correspond almost exactly

with those shown then. It is true that the type of pneumonia depends upon the nature of the organism which acts as a secondary invader and also upon the degree of lowering of resistance by the primary disease. We found that the nodular interstitial bronchopneumonia after epidemic influenza was associated with the influenza bacillus, while a similar condition after measles appeared to be caused invariably by a hemolytic streptococcus. The lesions of the muscles and those of the testicle were met with in many cases, and the latter have been described in detail by Mills.

Dr. Frothingham (closing): It would be treading on rather thin ice to make a diagnosis of the epidemic disease influenza just on the lesions in the adrenal glands, in the striated muscle and in the testicle. The typical distinctive lesion of this disease we think is in the lung, and the most striking gross appearance is the dilatation of the alveolar spaces and the intense congestion hemorrhage. In addition to this dilatation and intense congestion and hemorrhage there is the characteristic hyaline membrane which, of course, has been described previously.

SOME LESS FREQUENTLY CONSIDERED PORTALS OF INFECTION IN ARTHRITIS AND IRITIS

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The general principle that recurrent metastatic infections may result from chronic local infections seems well established, and the search for chronic hidden infections has become routine in the examination of patients, particularly those afflicted with arthritis and iritis. In many cases the removal of such chronic local infections is followed by freedom from recurrences of the metastatic lesions in eyes or joints and the relief of the patient from his disability. In other cases, in many of which the clinical appearances of the lesions in the joints are indistinguishable from those of the favorable group, the removal of chronic local infections, if found, fails to free the patient from recurrent lesions and the disease progresses. While much has been accomplished in the treatment of arthritis and similar metastatic infections, the study of the symptomatology and mechanism of chronic infections is by no means complete and offers an interesting field for investigation not alone in relation to lesions of joints and eyes but also in other branches of medicine, notably in dermatology. In inviting attention to portals of entry other than those of the conventional sites of chronic infection, it is recognized that the mechanism suggested is applicable to only a part, and perhaps a small part, of the unsolved group. The problem is, however, complex and efforts to solve a part may contribute to the solution of the whole.

Before passing to the consideration of the unsolved group, it will be of advantage to consider what happens in the patient in whom the removal of a tonsillar abscess, for example, is followed by free-

dom from a previously recurrent arthritis or iritis. The removal of the tonsils may occasion very little local reaction and the subsequent improvement in joints or eye is slowly progressive, so that after a few days the joint is free from pain or swelling and the residual functional disturbance is proportional only to the mechanical damage incurred by previous inflammation; the inflammatory reaction in the eye subsides gradually and return of vision depends on the degree of clouding of the media and mechanical disturbance resultant from the inflammation of the uveal tract. The favorable end-result is apparently effected by the removal of the local infection from which organisms can now no longer pass into the circulation and produce distant metastases.

In occasional cases in which the final result may be equally favorable the removal of the tonsils may or may not be attended by some fever and local inflammation. The effect on eye or joint is, however, more striking; the inflammation in the eye disappears within twenty-four hours, perhaps permanently; the effect on the joint may be as rapid but less easily observed. Such results are similar to those seen occasionally after the intravenous injection of foreign protein, and like them are probably non-specific. This sudden and remarkable improvement following the removal of a local area of infected tissue may be misleading, in that it may occur in patients in whom subsequent events show that the removal of this tissue did not effect a cure. Either the patient was the subject of multiple infections, of which only part was removed, or the cause of the disease in joint or eye entered the body from some other source.

A review of the group of cases in which search for and removal of chronic local infections failed to give favorable results will show that many belong to the composite group of arthritis known as arthritis deformans, in which other factors such as disturbances of nutrition, family predisposition and the persistence of infection in the joints themselves presumably play an important part in the continuation of the disease. In the present discussion it is desired to omit the group of frank arthritis deformans, not because the same principles may not apply here but because other factors just enumerated complicate the problem to a degree greater than in other types of arthritis and metastatic infection and tend to lead aside

from the issue of the portal of entry. There remain a considerable number of metastatic infections in which a thorough examination fails to give a satisfactory result in the search for etiology along the commonly accepted definition of focal infection. The prompt relief from metastatic infection which has followed the removal of chronic local lesions in favorable cases, the evident soundness of the general principle that recurrent bacterial invasion of the joints may originate from small areas of local infection and the name "focal infection" itself have led to the general clinical conception, assumed if not formally expressed, that all metastatic lesions of this sort, not preceded by one of the recognized general bacterial infections, enter the body from some preëxisting focus. It is consequently assumed that if the search is thorough and extensive enough a primary offending lesion may be found and removed. The search is prosecuted with more diligence than thought, and frequently patients lose teeth and other parts of their bodies without profit—to themselves—and to the discredit of a fundamentally sound but misinterpreted clinical principle.

Three less frequently considered portals of entry of recurrent infections present themselves: (1) The mucous membranes of the upper respiratory tract; (2) the tissues about the hila of the lungs and (3) the intestinal tract. In some of these the lesions are chronic and localized; in others the infection enters directly through mucous membranes without evident previous lesion.

The Upper Respiratory Tract. It is generally accepted that many infections begin as local superficial inflammatory lesions of the nasopharynx; if mild, they pass under the diagnosis of a "cold;" if more severe, they may become general infections, as in the severe streptococcal infections of 1917. In health, organisms which reach the buccal and pharyngeal mucous membranes are usually quickly removed, to a large extent by the mechanical flushing action of the secretions, as shown by Bloomfield.[1]

There is evidence, as he points out, however, that invasion of intact mucous membranes by bacteria may occur, and if at the time of such invasion the resistance of the body cells and fluids is lowered, or if the virulence or invasiveness of the organism is high, the invader may enter the blood stream. The experiments of Thiele

and Embleton[2] showed that general infection from the buccal mucous membrane occurs in guinea-pigs fed with virulent bacteria, provided the food is coarse enough to produce minor lesions of the mouth.

The invasion of the body by way of the buccal and pharyngeal mucous membranes is often accompanied by evidence of enlargement of regional lymph nodes, as in experimental infections with tubercle bacilli, and, clinically, regional lymph-node enlargement may afford the clue to the route of invasion in developed infections of other kinds. A group of acute infections characterized by initial pharyngitis, without tonsillitis, cervical and sometimes general enlargements of lymph nodes and spleen, which apparently is similar to the disease described years ago under the title of glandular fever, has recently been brought to the attention of pediatricians. While most of these cases occur in children a like condition is sometimes met with in adults, and occasionally in these a mild acute arthritis occurs. The arthritis, as well as the adenopathy, subsides rather promptly and therefore does not present a serious problem. The condition is, however, of interest as an example of probable systemic invasion through the pharyngeal mucous membranes and because the occurrence of the arthritis may suggest a search for other conventional sources of infection in arthritis. In patients subject to acute articular rheumatism, recurrences of actue rheumatic fever preceded by pharyngitis are sometimes seen in those whose tonsils have been removed as a prophylactic measure. Mild temporary arthritis occasionally follows acute streptococcal pharyngitis and colds in patients in whom there is no evidence of intervening sinus or other local infection.

The Lower Respiratory Tract. Aside from the chronic suppurative lesions of the lungs, which may be the source of distant metastases, there is an interesting group of cases in which the primary lesion is apparently at the hila of the lungs and in which other areas of chronic infection can be excluded with reasonable certainty. These cases have been more numerous in the years since influenza has been epidemic.[3]

The clinical features of this group are recurrent arthritis, attacks of erythema, with nodular swellings resembling clinically erythema

nodosum or erythema multiforme, frequently asthmatic seizures in adults not previously subjects of asthma and definite peribronchial thickening, particularly of the lower lobes, with sometimes enlargement of the lymph nodes at the hila of the lung, as shown by fluoroscopy and radiographs. The erythema, arthritis and asthma may occur singly or together. The pulmonary condition has usually followed bronchopneumonia and is not tuberculous. Periods of irregular fever of 100° to 103°, lasting to a few days to a week, occur, and with these febrile attacks come the erythema and arthritis. There is a moderate leukocytosis. Blood cultures, both aërobic and anaërobic, during the exacerbations of fever have usually shown no growth. Apparently the infection is resident in the peribronchial tissues and lymph nodes at the hilum of the lung, and is, hence, to be regarded as an unusual type of infection resident in a local lesion rather than as renewed invasion of the body through the respiratory mucous membranes. The diffuse erythema and asthma suggest a protein intoxication possibly derived from the infecting bacteria or the tissues affected by them. Several of these patients have greatly benefited by therapeutic doses of roentgen ray directed toward the tissues at the hila of the lungs.

The Gastro-intestinal Tract as a Portal of Infection. In certain of the acute specific diseases such as typhoid fever, and in some chronic infections such as tuberculosis of intestinal origin, the infecting organisms enter the body by way of the gastro-intestinal tract. The question as to whether other organisms which are not able to produce acute or chronic continuous infection with bacteremia can pass through the intestinal wall at intervals, enter the blood stream, lodge in the joints or other tissues and produce recurrent metastatic lesions similar to those produced by organisms resident in chronically infected areas is of considerable clinical importance. It is evident that, considering the large numbers of bacteria either temporarily or permanently resident in the bowel, the wall of the intestine must present, under normal conditions of health, a fairly effective barrier against bacterial invasion. When, however, these normal conditions are varied by inflammatory or other changes in the intestinal wall, or by modifications in normal resistance of the body to infection, it is conceivable that bacteria other than those

capable of causing a progressive bacteremia may enter the body through this portal. The problem is evidently concerned with (1) the passage of bacteria through the stomach and their fate in the small and large intestine; (2) the permeability of the mucosa of the intestine for small particles and bacteria, and (3) the survival of these bacteria in the lymphatics, lymph nodes and blood, and their subsequent lodgment in eyes, joints and other structures. As in other problems of infection the relative values of the ability of the invading bacteria to survive a progressively changing environment and the resistance of the body cells and fluids to bacteria are intimately involved.

In addition to gastro-intestinal symptoms which occur in the specific infectious diseases such as typhoid fever, the causal organisms of which usually enter the body by way of the gastro-intestinal tract, disturbances in stomach and intestine of varying degree with nausea, vomiting, anorexia, diarrhea or constipation are frequent in many other infections and are often merely expressions of functional disturbances of the intestinal tract coincident with actual infection elsewhere in the body. In some of these infections it is possible that the infecting organisms whose chief site of attack is the tonsil, nose or respiratory tract, pass down the gastro-intestinal canal and there act as direct excitants of inflammation and diarrhea. In another group the intestinal symptoms apparently result from the embolic lodgement of organisms in the intestinal mucosa, a mechanism similar to that in infectious arthritis. This seems to be true in certain cases of colitis in which a proctoscopic examination shows, in addition to the ulcers, small hemorrhagic areas in the mucosa with here and there beginning necrosis.

In infectious arthritis there are sometimes accompanying gastro-intestinal disturbances; in many, these disturbances appear to be secondary effects of the infection or to result from interference with normal exercise and food-taking; but in some the relation of symptoms is such as to suggest the possibility that the intestinal infection came first and that the arthritis resulted from bacteria which entered the body through the intestinal mucosa.

There are numerous case reports of iritis associated with gastro-intestinal upsets, constipation or diarrhea in which healing of the

iritis has apparently been hastened by treatment directed toward the intestinal tract, either by laxatives or modifications in diet, with the elimination or reduction of proteins, of fats or of carbohydrates. It is entirely possible that the real source of infection in some of these cases was in the intestinal tract as assumed, but in many no evidence is furnished to show that other of the recognized possible sources of infection were investigated and excluded. Further, it is possible that recovery may have been hastened by some of the measures alluded to, indirectly through the improvement of general nutrition and increase of bodily resistance to infection, and hence the fact of recovery following dietary or other treatment is not conclusive evidence of the direct etiologic relation of the intestinal infection to the iritis. It is thus difficult to prove directly in the individual case of iritis or arthritis that the infection which caused the metastatic lesion entered through the intestinal tract, but by demonstrating the absence of other sites of infection the probability of an intestinal portal of entry may be arrived at, providing the conditions under which invasion of the body from the intestine occurs are known.

The Permeability of the Intestinal Wall. The number and the varieties of organisms which enter the intestine are greatly reduced by the antiseptic action of the gastric juice. Normal stomach contents after an Ewald meal are usually sterile so far as concerns ordinary pyogenic bacteria; yeasts, sarcinæ and certain aciduric bacteria are frequently found in stomach contents of normal or increased acidity. Gastric juice (free HCl 20 to 40) or hydrochloric acid of corresponding strength in dilution of 1 to 16 will kill hemolytic streptococci in ten minutes and in higher dilutions up to 1 to 64 in one hour. Other common pathogenic bacteria such as the colon bacillus and Streptococcus viridans show a similar though somewhat less degree of susceptibility to normal gastric juice. This antiseptic action is not continuously effective throughout the twenty-four hours, however, for we were able to isolate hemolytic streptococci from the stools of 30 per cent of 85 patients with scarlet fever, although in some instances repeated attempts were necessary.[4] Organisms within the intestine thus may be recent arrivals as well as older residents.

The permeability of the wall of the intestine to small particles and bacteria within its lumen has been extensively studied in the investigation of the intestinal origin of tuberculosis, of pulmonary anthracosis, of conditions affecting the sterility of stored blood serum, of the route of invasion of certain infectious diseases and in the course of observations on antiperistalsis and on the mechanism of the absorption of fat. From experimental evidence in animals it appears that while the intestinal wall is not readily permeable to bacteria, or at least bacteria which do pass the first barrier are caught in the mesenteric lymph nodes, in exceptional cases a few organisms may pass into the blood by way of the thoracic duct.[5] It does not follow, of course, that the presence of such bacteria indicates a condition of sepsis, for they may still be destroyed in the blood or may perish in the tissues in which they lodge. When acute diarrhea is produced the experiments of Basset and Carré and others would indicate that the number of organisms entering the thoracic duct is larger. In a limited number of experiments in dogs after free catharsis we were not able to obtain such an increase, however. Williamson and Brown[6] were unable to recover Bacillus prodigiosus from a fistula of the thoracic duct in dogs by culture of the lymph after ingestion of the organisms regardless of diet or of previous catharsis.

The observations of McCarrison[7] on monkeys fed on deficient diet in which he found bacteria already present in the tissue spaces and within the bloodvessels of the intestinal wall at the site of hemorrhagic and ulcerating lesions of the intestine indicate the importance of the factor of injury to the bowel wall.

Blood Cultures in Ulcerative Colitis. In attempting to correlate the results of animal experiment with conditions met with in man it seemed advisable first to determine whether or not bacterial invasion of the blood could be demonstrated in ulcerative lesions of the intestine of man in the absence of fatal or serious sepsis. Ulcerative colitis or colitis gravis presents conditions in several respects suitable for such study. In addition to the abdominal distress, mucous, pus and blood in the stools, the ulcerative lesions of the bowel demonstrable by the proctoscope and at operation and necropsy, and the symptoms of malnutrition and anemia, patients

with ulcerative colitis frequently show periods of increased fever, occasionally chills, and in some cases recurrent arthritis. At necropsy also, enlargement of the mesenteric lymph nodes is pronounced. The arthritis and accessions of fever are suggestive of recurrent bacterial invasion, and it therefore seemed possible that a transient bacteremia might be demonstrable.

Through the courtesy of Drs. Sippy and Brown, Dr. Apfelbach and I have had the opportunity of studying 4 cases of ulcerative colitis, and in 2 of the 4 have isolated organisms in cultures from the blood during febrile periods. In both successful cases the organism isolated was a Gram-positive staphylococcus which produced a marked zone of hemolysis on blood-agar plates and was identical with a staphylococcus which occurred in overwhelming numbers in cultures of the stools of the same patients. Great care was exercised in providing necessary bacteriologic controls, and it is believed that the organisms which were present in repeated blood cultures, though in small numbers (not over two or three colonies on a plate) were present in the blood and were not contaminations. All four patients recovered.

In the experiments on animals, as well as in the observations in man, the conditions of bacterial invasion of the body in this type of infection are not those met with in sepsis, but rather those of the entry of occasional organisms which are detected at various points along their route of invasion. The difficulty of detecting occasional organisms and of determining their origin by excluding contamination is much greater than when experiments concern conditions of overwhelming sepsis. Experimental and clinical results, therefore, require the more critical evaluation before they can be accepted, and it is recognized that these clinical observations should be extended and repeated. Even when organisms have entered the blood stream it of course does not follow that they will be able to produce clinically recognizable metastatic lesions. Many will be destroyed *en route* in the blood stream provided the resistance of the patient to infection is not unduly depressed; when, however, conditions are favorable to the entry of organisms through the bowel wall and when at the same time, resistance to infection is depressed, it seems quite possible that metastatic lesions from an intestinal portal may occur.

It should be made clear that instances of this sort are few compared with the large numbers of metastatic infections of other origin, and that in perhaps the majority of instances in which temporary intestinal symptoms accompany recurrent metastatic infections they are secondary and incidental. The satisfactory demonstration of direct invasion through the intact intestinal mucosa of man by organisms which can cause arthritis without continued general infection presents difficulties which so far have not been overcome. That the intestinal tract may sometimes be the portal of entry of recurrent metastatic infection seems certain.

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INFECTIOUS JAUNDICE IN THE UNITED STATES
A SUMMARIZED REPORT

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Distribution. The occurrence of jaundice of an obviously infectious character has been recorded in the United States since 1812, the first epidemic having occurred in Norfolk, Va. in that year. From the chronological point of view the outbreaks may be arbitrarily divided into three periods. From 1812 to 1886, there are only 11 reports in the literature, and these record scattered outbreaks, 9 of which occurred in the South, 1 in Pennsylvania and 1 in New Jersey. Between 1886 and 1920, 51 outbreaks are reported, never more than 7 in one year, and these occurred in all sections of the country with the exception of the Pacific Coast States. Between 1920 and 1923, about 300 known outbreaks occurred, of which about 200 occurred in New York State alone during the state-wide epidemic of 1921 and 1922. The information which I have obtained regarding the disease has come partly from boards of health, but inasmuch as the disease is usually not reportable, mainly from correspondence with private physicians, Red Cross nurses and the authorities of institutions, like schools and colleges. Up to the present time, evidence has been obtained that the disease has occurred in every state of the union except Arkansas, Delaware, District of Columbia, Kentucky, Louisiana, Mississippi and Nevada.

Types of Outbreak. The types of outbreak which may occur in this disease may be described as follows:

1. The family outbreak.
2. The institutional outbreak.
3. The city outbreak.
4. The country outbreak.
5. The state-wide outbreak.

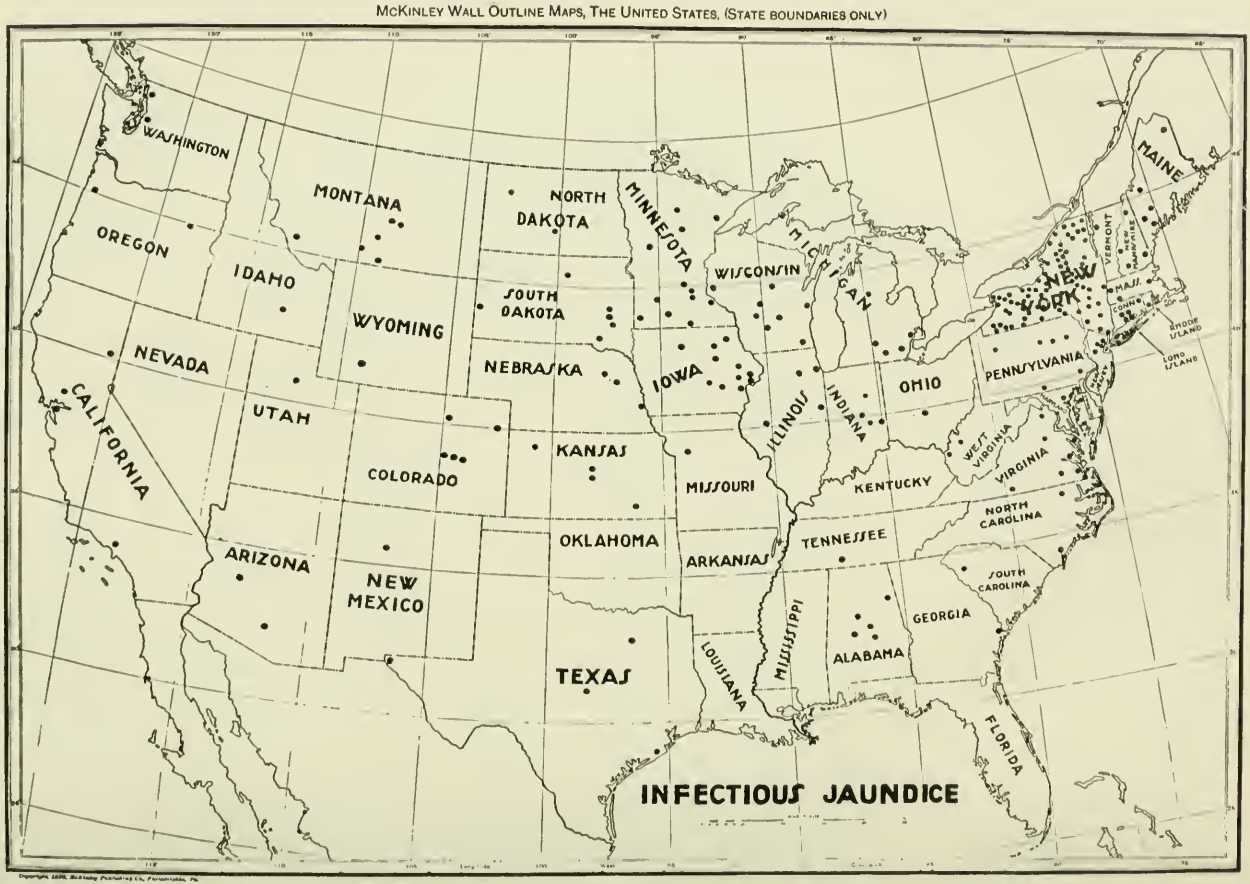

CHART I.—Distribution of outbreaks of infectious jaundice in the United States between 1812 and 1923.

In the family outbreak the disease may be confined to two or three members of a single family or to from 5 to 10 or more individuals in related or closely associated families. Such outbreaks are not at all uncommon, and even in large institutions the disease may affect only two or three individuals. The institutional outbreak may properly be compared to the family outbreak, because an institution merely represents family life on a large scale. A number of outbreaks have been observed in schools, colleges, jails and other institutions in which large numbers of people are brought together.

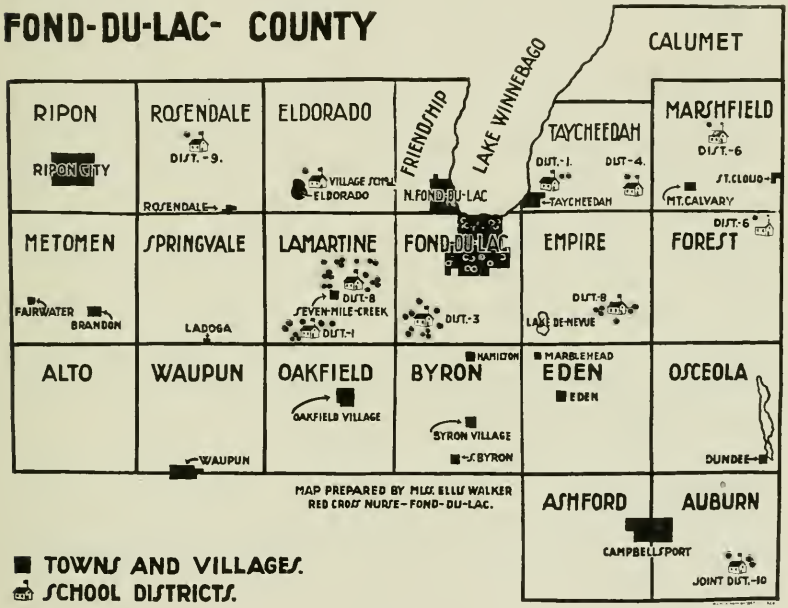

CHART II.—Distribution of a county epidemic. Both the undoubted and probable cases are included in the chart. The single dots represent single cases; where two or three dots are jointed together, this indicates two or three cases in a family. This chart well illustrates the relationship of the disease to the country school. (Prepared by Miss Ellis J. Walker, Red Cross Nurse, at Fond-du-Lac, Mich.)

It is not necessary to particularize as to what is meant by a city outbreak. I would merely point out that in such outbreaks the disease may be confined to a particular ward or a particular portion of a city rather than being uniformly diffused throughout the territory included in the city.

The country outbreak usually involves scattered cases spread over a considerable area, but outbreaks of the family type are by no means unknown in country districts.

But one definite state-wide epidemic has been reported up to the present, and that occurred throughout New York State during the fall and winter of 1921 and 1922.

Seasonal Incidence. The disease is essentially one with a well-marked seasonal incidence. An investigation of 50 outbreaks, concerning which satisfactory information was obtainable, showed that 14 per cent occurred in the fall, 22 per cent in the winter and 36 per cent extended over both fall and winter. In other words, 72 per cent of all the outbreaks occurred during the fall and winter months. Only 12 per cent occurred during the summer and fall, 6 per cent in the spring and 2 per cent throughout the entire year.

Age Incidence. The disease is also one which has a very definite age incidence. About 70 per cent of the cases occurred in children and young adults. In the 50 outbreaks mentioned, which covered approximately 3700 cases, 30 per cent of the outbreaks involved children only, 26 per cent involved mainly children, 8 per cent involved children and young adults and 6 per cent involved young adults entirely. In other words, 70 per cent of the patients in these 50 epidemics were children or young adults. Only 8 per cent of the outbreaks involved adults alone and in the remaining 20 per cent patients of all ages were concerned.

Method of Spread. With regard to the method of spread there is little doubt that direct contact with infected individuals is the way in which the disease is usually transmitted. An occasional writer states that there is no evidence of contact, but the overwhelming majority of those who have observed the disease unhesitatingly state that contact is the most important factor in its spread. There are instances where the outbreak of an epidemic could be definitely traced to the introduction of an infected individual into an uninfected district, and there are plenty of instances where infection occurred following known contact. There is some evidence that the disease may be transmitted by fomites. There is very little evidence that rats or other rodents have any direct relation to most outbreaks. It may not be generally known that there are large areas in this

country in which rats do not occur, and there are reports of outbreaks in such districts occurring at a period when other rodents, like the prairie dog and gopher, were hibernating.

Exciting Agent. It has been quite generally assumed that the type of infectious jaundice which occurs in this country is due to infection with spirochetes. This is a purely gratuitous assumption and is not based upon observation but upon inference. We have had excellent opportunities for bacteriological study of the disease at all stages in New Haven because it has appeared on several occasions among the nurses in the New Haven Hospital. Utilizing all of the usual methods, such as dark-field illumination, cultivation of the blood and urine and animal inoculation, we have never been able to isolate spirochetes. Dr. Wadsworth and his associates at the New York State Board of Health had a similar experience, and Dr. Symmers and others with whom I have corresponded have also failed to isolate spirochetes. Examinations of the duodenal contents have been made by at least three groups of observers, with negative results. In the cases in New Haven we have also studied the patients for the presence of organisms of the paratyphoid group, with negative results, so that it is my conviction that the organism causing the usual infectious jaundice of the United States is at present unknown. Inasmuch as infection of the upper air passages is a not infrequent accompaniment of the early stages, I would suggest that it might be profitable to examine the excretions from the nose and throat by the methods which have been used in connection with poliomyelitis. I wish to emphasize at this point that I do not deny that spirochetosis icterohemorrhagica occurs in this country. Indeed, I think it highly probable that it does occur, but I do not believe that the common non-fatal infectious jaundice is of this nature.

Symptomatology. I shall not devote much time to the symptomatology but will call attention to the main features, because I wish to discuss the relationship of this disease to certain other possibly allied conditions.

The incubation period is probably from seven to ten days, as a rule. There is evidence that it may be as short as two days and as long as twenty-eight days.

The clinical course of the disease is characterized by very great variability in different epidemics and in different patients in the same epidemic. In the marked cases the onset is usually sudden, with marked gastro-intestinal symptoms (anorexia, vomiting and constipation), with headache and pronounced pain in the back and limbs, with abdominal pain, usually epigastric and fever, which is usually not very high, but may be in young children. This period of febrile gastro-intestinal manifestations usually quiets down on the appearance of the jaundice, which generally appears about the fourth or fifth day, although it may be delayed as late as the twentieth day. The jaundice varies in intensity, is generally present from seven to ten days, but may disappear after a few hours or may continue as long as six weeks.

The usual physical signs are a coated tongue, a foul breath, a rapid rather than a slow pulse, an enlarged, tender liver and in some instances a palpable spleen. Occasionally the pulse may be slow and in some instances a skin eruption is present which rarely desquamates. The urine is generally concentrated, bile-stained and contains a trace of albumin. The feces are, as a rule, of the "putty" or "clay" type. The leukocyte count, judging from a few reported observations, is variable in the same epidemic, some patients showing a lack of leukocytosis or even leukopenia, while in others a marked leukocytosis is present.

It is to be noted that in many cases, sometimes in entire series of cases, fever may be absent, and it is also to be noted that in practically every extensive outbreak cases occur coincident with the outbreak which present all of the features of the disease except the jaundice.

Complications are quite rare, so rare that one is justified in suspecting that coincidence plays a part in their occurrence. Nephritis has been observed occasionally and in pregnant women abortion may take place. Recurrences are very rarely noted in this form of jaundice as contrasted with Weil's disease. Occasionally second attacks occur. Recovery may be quite prompt, but in many of the epidemics prostration is a marked feature and recovery is quite protracted.

A striking feature of the great majority of the outbreaks is a

complete absence of fatalities. In only 7 out of 64 outbreaks, concerning which adequate information is available, were there any fatalities. Practially all of the fatal cases occurred in young children or in pregnant women, and in the latter instance were accompanied by abortion. It is to be noted that the clinical picture in the fatal cases was essentially that of acute yellow atrophy of the liver or of a very severe intoxication, designated by some observers as cholemia.

Relation to Other Diseases. Aside from the question of etiology, the most important considerations in connection with this form of jaundice, which are suggested by its symptomatology and termination, are its relations to ordinary catarrhal jaundice, so-called, and to acute yellow atrophy of the liver. It is quite clear that the milder cases of the disease are clinically indistinguishable from ordinary catarrhal jaundice, and I would express the tentative opinion that ordinary catarrhal jaundice is also infectious and merely represents the sporadic type of the disease. This, of course, cannot be proved until the etiological agent is discovered.

Most observers of the disease claim that it bears no relation to acute yellow atrophy of the liver. However, Dr. Irving Lyon, of Buffalo, writes me that since the outbreak in New York State in 1921 and 1922 the pathologist at the Buffalo General Hospital has noted a very definite increase in the number of cases of acute yellow atrophy of the liver. Assuming that acute yellow atrophy is not a disease entity but rather a form of liver reaction which may be produced by a variety of infections and intoxications, I think it is fair to assume that the incidence of the disease might well be increased by the occurrence of infectious jaundice.

The study of this disease emphasizes the need of further investigations as to the seasonal incidence of ordinary catarrhal jaundice in this country and of further bacteriological study, not only of infectious jaundice but also of ordinary so-called catarrhal jaundice and acute yellow atrophy of the liver.

DISCUSSION

Dr. Joseph L. Miller, Chicago: During the epidemic of catarrhal jaundice in Chicago, about twelve years ago, one patient was observed

where the onset was exactly like that of the other cases during this epidemic. After five or six weeks, however, the jaundice failed to disappear, and, inasmuch as the patient gave a history of having had an attack of severe abdominal pain at one time, it was diagnosed as gall stones. It was thought that she might have a stone which had slipped into the common duct without pain. An operation was performed, but the gall-bladder was found to be normal. It was drained and for a week or more nothing but clear fluid escaped, this containing a considerable amount of mucus. After the lapse of ten days or more there were intermittent periods of bile-stained fluid, and finally this became continuous and the trouble cleared up. It is apparent from these observations that the cause of the jaundice was not in the common duct—that it was either in the smaller bile duct or else the liver cells had failed to pass the bile over into the biliary ducts.

Dr. N. E. Brill, New York: It pleased me to hear that Dr. Blumer was of the opinion that infection was the most frequent attendant of so-called catarrhal jaundice. There is practically no pathological evidence to prove that a catarrhal condition of the duodenum, attended by a catarrhal involvement of the common duct, produces the condition known as catarrhal jaundice. Medicine is too much swayed by the dictum of its masters. When the great leader, Virchow, said that catarrhal jaundice was induced by an obstructive plug of mucus in the common duct, resulting from a gastroduodenal catarrh, the medical world accepted that dictum as a fact, and so it has been transmitted and believed to this day, notwithstanding physiological and pathological evidence against it. In fact, this evidence to my mind is absolutely opposed to Virchow's assumption. It is very much more likely that the jaundice in these cases is the result of destruction of biliary capillaries, secondary to necrotic changes in the liver cells, as Eppinger pointed out, than to any other mechanism.

When the liver was examined by him in fatal cases such necrosis of its cells was invariably found. All of you, no doubt, as I have had experiences of catarrhal jaundice terminating in death. Acute yellow atrophy is the clinical terminating picture. Eppinger, who has had, perhaps, the largest clinical and pathological experience in these cases, showed that with the necrosis and atrophy of the cells of the hepatic sinuses, tears occurred in the capillary radicles which were intimately connected with these cells, as the result of which the bile escaped into the lymph channels adjacent, and this entered the circulation, giving rise to jaundice. Therefore, according to his views, the main pathogenic feature of the disease was the necrosis of the liver cells.

The seasonal appearance of catarrhal jaundice, of which there is no doubt, would suggest an infectious agency. Because the disease starts with malaise, epigastric distress, eructations and other symptoms commonly associated with disease of the stomach, it led to the assumption that a

catarrhal condition of the stomach and duodenum was the pathogenetic factor of the disease. Eppinger's view at least is consistent with physiology and pathology, and explains the relation of this disease to acute yellow atrophy of the liver, which unfortunately is an all too frequent cause of death in some of these cases, and indicates a toxic hematogenous origin of the disease or an infectious agency.

Dr. H. Noguchi, New York: I believe that these cases are often regarded as infectious jaundice, or Weil's disease. From the experimental standpoint I have had similar negative experience. In coöperation with Dr. Charles Herrman, of New York, I studied about 12 cases of epidemic jaundice among children in the spring of 1918. Blood and urine were examined (in some instances rather early in the disease) by the dark-field microscope, cultured and inoculated into guinea-pigs. No leptospiras were found by microscopical examination and none of the guinea-pigs ever showed any definite signs of infection. Cultures showed no growth and injections of the cultures into guinea-pigs failed to produce any infection. Blood sera from convalescent cases gave a negative Pfeiffer reaction with *Leptospira icterohemorrhagiæ*. At a later date a number of specimens of blood serum and urine from about 25 similar cases in New York State were studied in the same way (through the courtesy of Drs. Wadsworth, Roby, Longcope, Young and Nichols), but no relationship could be established between these cases and the leptospira of Inada and Ido.

On the other hand, among several specimens of blood serum from school children of Middletown, Indiana, sent me by Dr. Shimer, of the Indiana State Board of Health, one gave a positive Pfeiffer reaction with *Leptospira icterohemorrhagiæ*. These cases were observed by Dr. Waters, of Middletown, who found that the children had been drinking water from an old well. The well was drained, drinking from it prohibited and the epidemic among the children soon disappeared. While no definite experimental proof was obtained, there is a possibility that certain forms of leptospira found in stagnant water, as demonstrated in our recent studies, may produce a mild leptospiral infection in epidemic form. Since no systematic studies have been made as to the percentage of positive Pfeiffer reactions among mild but genuine cases of leptospirosis icterohemorrhagiæ (or Weil's disease), a negative Pfeiffer reaction in these cases of mild epidemic jaundice must not be taken to rule out infectious jaundice, and it is important to continue research along this line.

Should any cases prove fatal it would be important to study the pathological anatomical changes in the various organs, especially the liver, spleen and kidney. The blood picture—red and white counts and hemoglobin percentage—and the question whether the jaundice is due to hemorhexis or to abnormal hepatic function are also of great interest.

Dr. W. W. Ford, Baltimore: In one of the school epidemics which Dr. Blumer mentions the material was obtained for examination in our laboratory and we have had many conferences in regard to it. Our general impression of this outbreak, which occurred in Virginia, is rather different from that of Dr. Blumer. We felt that the portal of entry was the gastro-intestinal tract. No cases suggested respiratory infection. The incubation period was very much extended in some instances; there were well-marked cases with an incubation period of thirty to forty days. Our results coincided with those of other laboratories. In one case we did get paratyphoid organisms from the duodenum, but I do not believe it was really a paratyphoid infection. One method of study would be that of early cases by duodenal washings. The parasite seems to attack primarily the gastro-intestinal tract. Dr. Dowell has records of cases in Nova Scotia which occurred as a summer outbreak.

Dr. Norman Gwyn, Toronto: I saw a large number of epidemic cases several years ago. I agree with Dr. Blumer that the disease may be so mild as to simulate catarrhal jaundice or so severe as to show a picture of acute yellow atrophy. At some autopsies it was difficult to think we were not dealing with acute yellow atrophy. From some of the milder cases we were able to transmit the disease to guinea-pigs, and unless they were lying in their behavior these animals showed a very interesting picture. We may have been dealing with a very active type of infection and one in which the infecting agent was present in large numbers. Some of the cases came in with such diagnoses as cholecystitis or cholelithiasis, cases in which it seemed that the first attack of their infection had blown over in a few days, but cases in which pain and fever had later developed together with general symptoms which made us suspect something more than an ordinary gallbladder or gall stone attack.

From one of these cases at the height of the disease we took 10 cc of blood, separated the serum from the corpuscles, centrifuged it and examined the precipitate with a dark-field illumination, and were successful in finding several actively moving spirochetes. If one is interested in this line of work he will find that it will pay to inoculate an animal with blood taken during the active febrile period, as after the first two or three days the chances of finding the organisms are remote.

In the infected guinea-pigs one may find spirochetes in the blood as taken from the tip of the ear, and at an autopsy on these animals the smear from the liver may show spirochetes as plentiful as in the smear from the gums in a case of pyorrhea; huge swarming masses may actually be demonstrated. We never had any success in our attempts to demonstrate spirochetes in the urine.

In regard to clinical symptoms one may say that they range from those of acute catarrhal jaundice to those of rapidly fatal acute yellow atrophy.

In one of our cases in which there had been abdominal pain and vomiting the diverticulum of Vater was swollen and occluded in conjunction with acute inflammation of the duodenum.

The most interesting thing in the clinical picture is the acute myositis; in one of our cases it was debated whether both thighs should be incised for the supposed collection of pus and in many cases the acute muscle pain was a very definite feature of the disease.

During the epidemics of jaundice in the army we had some deaths from a rare form of myositis, and in Boulogne it was demonstrated by Sir Bertrand Dawson and his assistants that the spirochetes of infectious jaundice were present in certain cases of fever without jaundice and that myositis had been a part of the disease picture in these cases.

It is interesting to note that in Japan myositis has been known to exist to a much greater degree apparently than elsewhere, and that it is here also that the greater number of cases of infectious jaundice are seen.

Dr. Henry Koplik, New York: The impression is that this jaundice is a distinctly toxic affair. In some cases certain foods, not fresh, such as fish, has caused infection in families of several children. There is enlargement of the liver, some temperature, abdominal pain and enlarged spleen. There is bile pigment in the urine. In some cases infection of children has been reported, due to the water supply, but though the cases were evidently toxic, no bacteria were discovered.

Dr. Blumer (closing): In regard to Dr. Brill's remarks about catarrhal jaundice, I agree that the medical profession has been dominated by Virchow's statement up to the time of Eppinger's work. There does not seem to be obstruction of the ducts, but there is an enlarged and tender liver. In these outbreaks there are many cases where jaundice does not occur at all. There is plenty of evidence that so-called catarrhal jaundice is seasonal. This can be found in the records of the Japanese Navy and the German Army.

In reply to Dr. Noguchi: In a great majority of the reported cases where mention is made of the urine, this contains not only bile but a definite amount of albumin, although not more than would be associated with other febrile diseases. In the literature a few cases are complicated by nephritis. With regard to hemorrhagic jaundice this is lacking in the vast majority of reports, differing thus from Weil's disease. In a certain proportion of cases there was nosebleed, but hemorrhagic tendencies were lacking. This looks as if the cases were not of a spirochetal nature. We are at a great disadvantage as to the pathology, because there were few fatal cases and autopsies. In the European literature a few autopsies were reported and the findings in young subjects were the same as those of acute yellow atrophy of the liver.

In reply to Dr. Ford: The upper air passages were evidently the portal of entry in a certain proportion of cases, but I do not wish to give the impression that this was the only mode of infection. In some instances infection probably takes place through the gastro-intestinal tract. There are epidemics in which duodenal washings have been investigated. At the Mayo Clinic this was done, but the result was negative.

In regard to Dr. Gwyn's remarks: I feel that cases seen in France were hemorrhagic icterus, or Weil's disease. In the European form it is more difficult to isolate spirochetes than in Japan.

In regard to Dr. Koplik's remarks: I cannot answer his question definitely; some of the cases may be toxic in origin, but I do not think we can explain widespread epidemics as of toxic origin because the patients are not all under the same food conditions.

EXPERIMENTAL EPIDEMIC ENCEPHALITIS AND EXPERIMENTAL HERPES[1]

By SIMON FLEXNER, M.D.
NEW YORK

Ever since 1918–1919, when the world first became aware of the prevalence of epidemic or lethargic encephalitis, efforts have been made to induce the disease in animals in order that its nature might be more closely and accurately investigated.

Indeed, Wiesner had carried out an inoculation test with portions of the central nervous tissues taken from a fatal instance of Economo's first series of cases, and believed not only that he had induced the experimental disease in a monkey, but also that he had cultivated a coccus which was to be regarded as the infectious agent or microörganism of the malady.

This early observation of Wiesner has not been upheld by later investigators, and in the same catagory with it belong the experiments with similar cocci described more recently by Rosenow in this country and by some other writers on the subject.

It is interesting to note that the experimental studies so successfully carried out in epidemic poliomyelitis a decade or more ago supplied much of the inspiration for the investigation of epidemic encephalitis now still being pursued actively.

This influence can be detected in the experiments reported by the group of workers at Mt. Sinai Hospital in New York, who are to be credited with the opening of epidemic encephalitis to experimental exploitation.

Loewe, Strauss and Hirshfeld have published several papers in

[1] From the Laboratories of the Rockefeller Institute for Medical Research, New York.

which they have described their experiments in detail. According to them, monkeys, but rabbits especially, are subject to subdural inoculation with the brain tissue, cerebrospinal fluid and filtered nasopharyngeal secretions taken from persons the subjects of epidemic encephalitis, to which the animals succumb. The symptoms induced correspond more or less closely with those observed in cases in man. The infection produced in rabbits is communicable indefinitely in series to other rabbits, and the infectious agent is, according to them, a minute anaërobic organism, filter passing, and obtainable in a manner similar to that of the so-called globoid bodies of poliomyelitis, which bodies they more or less resemble. The several materials derived from human cases are said to be so readily inoculable upon the rabbit that the inoculation method is applicable for purposes of diagnosis.

These positive results, on the surface so readily obtainable, have not been generally confirmed. The fact is interesting and may prove to be significant that while a few investigators have been able in some degree to repeat the Mt. Sinai Hospital work, others have failed to do so. In no instance has the work in its entirety been confirmed. Thus in about 30 tests with various materials taken from cases of epidemic encephalitis, Levaditi and his coworkers have reported success in 2—once with nervous tissues and one with nasal secretion; while Doerr and his associates have reported, among a large number of failures, 3 successes, once with cerebrospinal fluid and twice with nervous tissues, and Schnabel another instance. To this relatively inconsiderable number of successes may be added a few isolated examples of so-called successful transmissions which stand, however, on a less secure because less convincing experimental basis.

Amoss and I began, in 1919, to make experimental inoculations of animals with a view to reproducing epidemic encephalitis in animals in the manner of the production of experimental poliomyelitis. We first employed monkeys and later other animals—the rabbit, guinea-pig, sheep, etc. In choosing the sheep we were influenced by the work of Cleland and Campbell on so-called Australian X disease. We failed entirely to secure a successful transmission with unfiltered and filtered emulsions of the nervous tissues of fatal human

cases. The brain, in these cases, when examined microscopically showed typical lesions of epidemic encephalitis located chiefly in the basal ganglia.

While our unsuccessful inoculations were still under way the first of the Mt. Sinai results was published, and hence Dr. Amoss and I extended our injections so as to include first filtered nasopharyngeal secretions and next cerebrospinal fluid taken from cases of epidemic encephalitis.

Notwithstanding the fact that the materials and the manner of inoculation seemed to be above suspicion, successful infection was denied us. Now and again an inoculated animal, after showing symptoms more or less referable to affection of the central nervous organs, succumbed. On autopsy, meningitis, brain abscess and hemorrhage were occasionally found, but were attributable either to a secondary bacterial infection or to trauma. In doubtful instances reinoculation was practised to make sure that transmission of a condition resembling epidemic encephalitis was or was not secured.

It was not until 1923 that one of us (Flexner) met with what appeared to be a successful transmission. In order to extend the scope of the experimental study a wider variety of material was used for inoculating rabbits. Chief among these materials was cerebrospinal fluid obtained from as many sources as possible. The Presbyterian and Babies' Hospitals and the Neurological Institute in New York kindly coöperated. Dr. Amoss, on his part, assisted at the Johns Hopkins Hospital in Baltimore.[1] No selection of cases was made; the cerebrospinal fluids, proven to be sterile, coming into the clinical laboratories for purposes of diagnosis were injected subdurally into rabbits. The fluids included many specimens from cases of syphilis, of brain tumor and of less common nervous and other affections. They included also cases diagnosed as epidemic encephalitis.

With the miscellaneous fluids, 2 or 3 rabbits were injected; with the fluids from cases of clinical encephalitis, 4 or 5 were inoculated. The rabbits were observed over many months. Any detected illness

[1] The details of these studies will appear in the Journal of Experimental Medicine.

was closely followed. The rectal temperature of sick animals was taken; they were inspected twice daily; in case of death, autopsy was performed promptly, cultures and films of the nervous tissue were made, material was taken for histologic examination, for glycerolization and also in promising instances immediate reinoculation was practised.

As stated, a single successful transmission to the rabbit of a disease resembling in all respects the condition called experimental encephalitis was secured. This success was attained with a specimen of the cerebrospinal fluid derived from a male, aged fifty-one years, suffering from cerebrospinal syphilis. The patient had been under treatment at the Presbyterian Hospital, and had been subjected among other measures, to intraspinous injections of arsphenaminized serum. On January 4, 1923, 2 rabbits received each subdurally 0.35 cc of the clear fluid showing globulin by Noguchi's test. On January 13, 1 rabbit showed tremor, turned in circles to the left (site of inoculation), presented opisthotonos and had a rectal temperature of 105.6° F. The animal died the next day (January 14). No lesions were discovered in the organs; the brain was sterile in ordinary cultures. With this rabbit a series of inoculations in rabbits and other rodents (guinea-pig, rat, mouse) has been carried out. The active brain tissue has suffered no diminution after many transfers. The active material is filterable and glycerol resistant. Monkeys do not respond to subdural inoculation with an emulsion of the active rabbit brain. The second rabbit remained permanently well.

On February 2 a second specimen of cerebrospinal fluid from the same patient was injected subdurally into 5 rabbits, but without result.

We may therefore fairly claim to have obtained a transferable "virus" from the cerebrospinal fluid, which induces an encephalitis in rabbits and is transmissible in indefinite series to rabbits and to other rodents. The question which now arises is whether this "virus," although secured from a case of cerebrospinal syphilis, is identical with the so-called "virus" of epidemic encephalitis? We believe that, as tested by all the known criteria, it is indistinguishable from the latter. We have, through the courtesy of Dr. Levaditi

and Prof. Doerr, who kindly sent us glycerolated brain tissues, been able to make the necessary comparison leading to this conclusion.

We feel that too little has been made in this country of the symptoms which arise in the rabbit as the result of infection with the active material or "virus" we are considering. The symptoms are varied and striking. The outstanding ones are high temperature (up to 107°), muscular excitation—tumors, turnings, somersaults—paralyses, salivation and sometimes, though rarely, lacrimation and retention of urine. Death is often sudden and through convulsions. According to the strain and dosage of the "virus" the symptoms arise quickly (two to three days, and death is swift) or more slowly (eight, ten, twelve days, and death is delayed).

The brain shows lesions which are held to involve (*a*) the meninges, (*b*) the cortex variably, and (*c*) the basal ganglia chiefly and more constantly. There is no doubt that the severity of the meningeal reaction and of the cortex depends in part upon the nature and manner of the inoculation: a suspension of active brain tissue excites a severer local reaction than, for example, a filtrate. Infection induced by intravenous, intratesticular or intranasal introductions of the "virus" is accompanied by brain lesions, but the local effects mentioned are absent.

The domestic rabbit, however, introduces a factor into the question of the brain lesions attributable exclusively to the action of the "virus" which is disconcerting. The important fact is that in this country, at least, the domestic rabbit as used for experimental purposes shows not infrequently evidences of affection or infection of the brain, with which our experimental procedures have nothing to do. Several years ago Reasoner encountered lesions in the brain of Treponema pallidum infected rabbits and mistook them for syphilitic manifestations. A little later, Bull showed that they occur accidentally in rabbits used for experimental purposes, and more recently Oliver has repeated Bull's observation and warning. Brown and Pearce, at the Rockefeller Institute, frequently encountered the lesions in rabbits with experimental syphilis, tumor, etc., and the writer has been acquainted with them for many years. In following the experimental work on epidemic encephalitis, he has from time to time been impressed with the similarity of the brain

lesions described and figured by different investigators with these so-called "spontaneous lesions." This agreement is perhaps most striking in the articles published by Kling and his coworkers in Stockholm. It is detectable in the illustrated papers of the Mt. Sinai workers and in certain of Levaditi's descriptions.

Having in mind the confusion brought by this factor into the experimental investigation of epidemic encephalitis, and as will appear, in that of febrile herpes also, the writer requested Dr. McCartney, at the Rockefeller Institute, to make a special study of the subject of the accidental occurrence of brain lesions in the laboratory stock of rabbits. He investigated about 300 animals. They were such rabbits as died of snuffles or other disease before inoculation, or as were sacrificed as healthy to obtain kidney tissues for Smith-Noguchi anaërobic cultures or employed in connection with experiments on influenza, tumor transplantation, pallidum infection, etc. Suffice it to say that in one-half (50 per cent) of the rabbits examined local lesions were detected in the meninges and cortex or in the basal ganglia. The brain removed at autopsy was often examined in frozen section by Dr. McCartney, and when found to contain the lesions, employed for subdural injection of supposedly healthy rabbits. In no instance was a transmissible acute infection induced, although the inoculated animals might subsequently show lesions of the order of those present in the brain used for injection. The lesions were regarded, of course, as preëxisting and not due to the inoculation. This high percentage (50 per cent) is in surprising agreement with the figures of brain lesions in encephalitis infected rabbits as given by the Mt. Sinai workers and by Kling. In a very recent paper, Doerr, in Basel, has described a form of this accidental lesion not infrequent in the United States, and with which certain of Kling's lesions are in accord.

The difficulty introduced into the subject of experimental epidemic encephalitis in the rabbit from this source is further increased by another set of recent observations, of very great interest, to which we must now attend.

In 1913, Grüter, an ophthalmologist, discovered that herpetic keratitis in man is communicable to the rabbit. If, for example, the cocainized rabbit cornea is lightly scarified and secretion from

a case of herpetic keratitis introduced into the conjuctival sac, a similar herpetic condition accompanied by a severe conjuctivitis arises in the rabbit. This observation, although not published until 1920, became known to other ophthalmologists, who repeated and confirmed it. Löwenstein, also an ophthalmologist, first confirmed and also extended the findings of Grüter. Among other things he found that the inoculated but healed herpetic cornea of the rabbit was refractory to a second infection and that all forms of febrile herpes would induce the keratitis in the rabbit.

Among those who early studied experimental herpetic keratitis was Doerr, who made the important observation that now and again the inoculated rabbits developed symptoms of encephalitis to which they succumbed.[1] He became impressed with the resemblance between this herpetic encephalitis and the descriptions of experimental epidemic encephalitis, and as soon as opportunity offered made cross-immunity tests which indicated relationship between the two experimentally induced conditions.

Two further observations which soon followed have singnificance in this connection: First, Blanc, of Athens, found that the brain of rabbits succumbing to herpetic general infection would excite an herpetic keratitis, and next Levaditi determined that the scarified cornea of the rabbit reacted to inoculation of the brain of animals succumbing to experimental encephalitis with herpes-like vesicles and the brain both of the herpes and the encephalitis rabbit smeared on the scarified abdominal skin of rabbits induced a herpes-like vesicular eruption.

The two lines of experimental investigation, namely, of epidemic encephalitis and of febrile herpes, have now converged. The similarities are increased in view of the filterable character of the herpes virus, its glycerol resistance and the general cross-immunity reactions displayed by the active materials from the two sources.

It is obvious, therefore, that a new field of exploration has been opened up in respect to the so-called filterable class of infectious agents or viruses by the discoveries made in connection with epidemic encephalitis and of febrile herpes. To which of these two active agents does the one obtained from the cerebrospinal fluid of

[1] These symptoms are indistinguishable from those given for the virus of encephalitis.

the case of neural syphilis belong? I stated that cross-immunity tests showed it indistinguishable from the encephalitis virus of Levaditi. I may now add that it induces vesicular keratitis and dermatitis in the inoculated rabbit, and on cross-testing displays the same immunity reactions as does the herpes virus.

The question of the precise nature of our virus we are leaving open for the moment, just as we are leaving to future determination the question whether the infectious or etiological agent of epidemic encephalitis has in fact been discovered.

DISCUSSION

Dr. Hans Zinsser, New York: Dr. Flexner has shown great conservatism in his conclusions. A great deal of confusion has resulted from the fact that in dealing with herpes virus we have concluded that it was the same substance as the virus of encephalitis. There is also a filterable virus of fowl pox. So little is known of filterable viruses that it is unsafe to draw conclusions. We easily infected a rabbit on the cornea with herpetic virus from a common cold. We kept the strain running along, and have had one strain from March, 1922, but we have discontinued the work as regards herpetic virus. In human beings the virus may be present in the saliva when there is no herpes. We had the same unsatisfactory results as Dr. Flexner did when we tried to transmit encephalitis. We had to throw out a great many rabbits on account of mixed infection even after two or three passages. Merely planting a piece of brain was not enough to give inoculation. The brain must be mashed up and an emulsion made. We have 3 cases, valid at present, 1 at the third generation and 1 at the fifth generation. There is a tremendous irregularity in individual rabbits. I agree with Dr. Flexner that these viruses are a new group of organisms, but I do not believe encephalitis and herpes are the same.

Dr. Emanuel Libman, New York: It is evident that a number of filtrable viruses will be cultivated and that further study will be necessary to decide definitely which are the causes of the diseases in which they are found.

In the work done by Strauss, Hirschfelder and Loewe, on epidemic encephalitis, there was fortunately no trouble because of the occurrence of spontaneous lesions in rabbits. All the controls were entirely negative. The control cases were selected from the surgical side of the hospital. This was fortunate, as carriers might otherwise have been used erroneously as

controls. None of the control patients, as far as is known, had suffered from herpes. The studies of Doerr indicate that the virus of that condition persists at the most six weeks after recovery.

Drs. Loewe and Zeman cultivated from cases of influenza a filtrable organism, a report on which was made very shortly after that of Olitzky and Gates. Dr. Olitzky has stated that the organism appears to be identical with his own. When the virus or organism is inoculated intradurally in rabbits no lesions are produced. When injected intratracheally, characteristic thromboses are found in the capillaries and arterioles in the parenchyma of the lung and in the bronchi. These thrombi consist almost entirely of blood platelets. On the other hand, the virus and organism found in association with epidemic encephalitis produce no such lesions in the lung after intratracheal injection, and do cause encephalitic lesions on intradural injection.

A CONTRIBUTION TO THE PATHOLOGICAL PHYSIOLOGY OF BOTULISM[1]

By CHARLES W. EDMUNDS, M.D.

AND

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During the past few years there has been an increasing interest taken in the form of food-poisoning known as botulism. The condition is by no means a new one, as it has been recognized and described for almost two hundred years. In this country, however, numerous outbreaks have occurred recently, and these, on account of certain characteristics, have served to call the attention of both the profession and the laity to the seriousness of the intoxication. That the condition appears in widely separated districts, that it frequently attacks several members of a family, and that its appearance is sudden and its mortality high are all facts which combine to give the outbreaks somewhat of a spectacular nature. With all this interest, however, it has not been possible to arrive as yet at an agreement as to the pathological foundation for the clinical manifestations of the intoxication.

In one of the most extensive monographs which has appeared on the subject in recent years, namely, that by Dickson,[1] it is pointed out that there are two views as to the pathology of the disease, but that, as yet, the cause of the symptoms or the way in which the paralysis of the muscles is produced is unknown. Dickson holds that one of the lesions which is characteristic of botulism is the thrombosis in the bloodvessels of the brain, which was described by

[1] From the Pharmacological Laboratory of the University of Michigan.

Wilbur and Ophüls as occurring the Stanford fatal case. It was found also in three of the fatal cases described by Dickson, but, as he says, the importance of the thrombi in relation to the clinical symptoms is unknown. The other view is that the pathological lesion consists of degenerative changes in the nerve cells in the motor nuclei, a view advanced by Marinesco and supported by other later workers.

There are serious difficulties connected with accepting either of these views as representing the whole story of the pathology. For one thing, it is hard to explain on the thrombosis theory that there are no sensory symptoms described as an essential part of the disease. This is strange, inasmuch as the thrombi are supposed to be widespread in the brain vessels. Then, also, the relatively rapid and complete recovery which is sometimes seen in serious cases is hard to understand if the symptoms are due to thrombi shutting off the circulation to the nuclei in the brain. Finally, thrombi have been found in only a certain number of cases which have been examined pathologically.

The theory that the underlying trouble is due to degenerative changes in the nerve cells is quite attractive, but the difficulty here is that the distribution of these lesions does not correspond to the motor paralysis. For instance, the third cranial nerve is perhaps the one which clinically shows the most constant involvement, and yet here Marinesco found the least severe nerve-cell change. These and other facts, which are discussed fully by Dickson, have led him to conclude that there must be some other factor involved than those mentioned. He discusses the possibility that the toxin may act upon the terminations of certain nerves and suggests a similarity between poisoning by belladonna and by botulinus toxin. He cites the dilatation of the pupil, the drying up of the secretions and the inhibition of the intestinal movements as points of similarity, but it must be pointed out that the comparison between the two intoxications is only seen upon very superficial examination. For instance, the mydriasis and the drying of the secretions are by no means seen in every case of botulism; the reverse condition of the secretions is by no means uncommon. Then, and perhaps most important, atropine has no action upon the terminations of the motor nerves in

warm-blooded animals, whereas the paralysis of the voluntary muscles is characterisitic of botulism.

As regards such a peripheral motor paralysis, a recent paper by Dickson[2] says that in dogs, cats and rabbits no such paralysis exists —that the motor nerves are normal. He does find some block in the vagus, but the same is of an unstable nature, being only temporary.

Finally, as an explanation of some of the vascular changes, the possibility of an action of the toxin upon the endothelium of the vessels is suggested. That there may be such an action is supported by the investigations of Warthin,[3] reported recently.

A survey of the literature since the paper by Dickson shows many important contributions to the subject—such as reports of cases; some with autopsy findings, others with reports as to the various aspects of the bacteriology of the condition—but none, so far as our present purpose is concerned, adds anything material to that given in the general discussion above. Many cases have been described in the literature as botulism which are clearly something else. As an example, a recent case[4] may be mentioned:

A child, ill six weeks, showed, among other symptoms, severe pain, delirium, rigidity of neck, muscular twitchings, knottings—patient becoming rigid, head bowed back, paroxysms of pain, etc. Such a case is described as botulism, but the postmortem examination discloses leptomeningitis, internal hydrocephalus, etc.

Such a report does not add much to our knowledge of botulism.

It should be emphasized that the essential symptoms of botulism are motor—a paralysis of certain nerves or mucles, but a loss of motor power in any case. There is early involvement of the third nerve and finally paralysis of all the extrinsic muscles of the eye, difficulty with swallowing and talking, due at least in part to paralysis of the pharyngeal muscles and impairment of the movements of the tongue. Progressive muscular weakness may become so marked as to lead to inability to raise the arms and legs or even the head. There is marked immobilization of the face muscles leading to a mask-like expression. The increasing weakness of the respiration is well described by Fischer[5] who speaks of the paralysis of the diaphragm with the disappearance of the abdominal type of breathing. He also speaks of the gradual loss of movement in the lower thorax

with the movement of the upper ribs becoming slighter and slighter until respiration stops from paralysis of the "respiratory center."

One of the best of the recent descriptions is that by McCaskey,[6] who reports 7 cases with 4 deaths. The interesting point in this report is that McCaskey states that while histological changes have been described in the central nervous system, the clinical picture appears to be that of a peripheral paralysis. He compares the clinical picture to that produced by diphtheria, a disease which produces its paralytic manifestations by an action on the peripheral nerves. While struck by this similarity suggesting a like pathological basis, McCaskey is compelled to accept the general view of a central lesion.

From this short discussion of the recent literature of the subject it will be clearly seen that there is no explanation of the symptoms of botulism that is generally satisfactory. We therefore decided to investigate the subject, using the ordinary pharmacological methods, and to see whether these would add anything to our knowledge. The toxin employed has been very generously furnished us by Prof. Herbert W. Emerson, of the department of bacteriology of this University, and was prepared by him from material obtained from different sources. While all the toxins supplied by Prof. Emerson acted essentially alike, some were stronger than others, but by far the most toxic was prepared from bacilli isolated from the intestinal contents of a patient dying in Grand Rapids as a result of eating spinach. The second sample of toxin was prepared from bacilli isolated by Dr. Krumwiede from olives concerned in the New York cases of poisoning. Sample three was from bacilli isolated by Dr. Emerson from the New York olives. The above were all of Type A. The fourth sample was toxin of type B, prepared from bacilli isolated from cheese, by Miss Nevins while with the New York State Laboratories at Albany.

With these toxins, but mainly with the first mentioned, we have carried out experiments utilizing frogs, guinea-pigs, rabbits, cats, dogs and chickens. Up to the present time our experiments with frogs have been negative, but we intend to carry these investigations further. All the animals mentioned (except the frogs) were injected intraperitoneally, the guinea-pigs with doses averaging about 0.01 cc, which dose would kill in about twenty-four hours. The cats

were much more resistant. Two or three injections of 5 cc each were required to kill in a week's time, and, as the cats usually would not eat after the symptoms were developed, it was hard to tell how much of the weakness was due to the toxin and how much to lack of food. To obviate the difficulty larger doses of 10 cc each were given, and two such doses would, on the average, kill a cat within seventy-two hours. Dogs were also resistant. After a little experience we found that an injection of 10 or 15 cc followed by a second dose of the same size would usually produce symptoms in thirty-six hours, and a total of 30 cc would usually kill in forty-eight hours. Cocks were more susceptible; 0.5 cc. of a good toxin injected into the breast muscles usually killed in from twenty-four to forty-eight hours.

Considering now the results obtained on the mammals, it would not seem necessary to describe the symptoms for each species in detail, as they have been given by earlier workers. One of the earliest and most characteristic symptoms seen in guinea-pigs, rabbits and cats is the great relaxation of the abdominal walls. They seem to offer no resistance to the palpating hand. Well-nourished cats undergo quite a change in their appearance as their flanks apparently fall in, giving the impression that they are starved. Perhaps the next symptom to attract attention is the change in character of the respiration. Normal cats, sitting quietly, show the abdominal type of breathing. With each downward excursion of the diaphragm, pressing as it does upon the contents of the abdomen, the sides of the abdomen are pressed outward. In botulinus cats, however, the type of respiration changes early. Doubtless due to paralysis of the diaphragm, it becomes passive and, the accessory muscles being called into play, the thorax is raised, creating an increased negative pressure in the abdomen, thus pulling in the non-resisting abdominal walls. The type of movement is thus completely reversed, giving quite a striking respiratory picture. As the intoxication progresses the thoracic muscles become weaker and weaker, so that the phenomenon described becomes less marked until the respiration stops. The muscular weakness, which first appears in the hindlegs, is a later manifestation than the respiratory disturbance. This too becomes progressively greater and involves

the forelegs, but it rarely passes into a total paralysis, as just before death the animal may be able to make movements. It may try to turn over or even to make efforts at standing. The movements of the head do not seem to be interfered with seriously until very late in poisoning, except of course in chickens, which show the characteristic limber neck due to paralysis of the neck muscles. As to the secretions there was nothing very characteristic. Certain of the cats were salivated and the saliva would slowly trickle from their mouths. This symptom was not common in dogs, in which the secretions were apparently lessened, as it was quite common for these animals to have a dry, rasping cough as though they were making efforts to expel dry mucous, but it was always without avail. This dry cough was not a common symptom with cats, but was occasionally found. The symptoms from the gastrointestinal tract also differed in different animals. Constipation seemed to be the rule with dogs, but diarrhea was very common in cats, and especially in chickens. In man, as is well known, obstinate constipation is the rule in botulism.

Passing from this general discussion of the symptoms, we shall take up a closer analysis of their causation. As constipation is such a prominent symptom as just mentioned, we decided to first investigate the condition of the gastrointestinal tract. Guinea-pigs, rabbits, cats and chickens were utilized for the purpose. The animals were injected as stated, and then as the intoxication progressed they were carefully watched until they died, so as to get them at the moment that respiration ceased. At that time the chest and abdomen were opened and sections were cut from the esophagus, stomach and upper and lower intestine. These were placed in cold Ringer's solution, and in case they were not to be used at once the container with the tissue was placed in a refrigerator. When needed, the pieces were washed and then placed in warm oxygenated Ringer's solution and arranged in the usual manner to record the movements upon a kymograph. Addition now to the bathing fluid of the drugs usually used in such an experiment, namely, epinephrine, pilocarpine, atropine, physostigmine, barium and pituitary extract, showed that in every case the addition of the drug was followed by a perfectly normal response—contraction or relaxation, as the case might

be. The result in each tissue from each animal was of course compared with normal controls. The only difference to be found was in the duration of life of the tissue under examination. As is well known, normal tissues preserved in this manner will retain their vitality and activity for hours, while we found that the tissues removed immediately after death caused by botulism would remain active for only a short time—for half an hour usually, but rarely for an hour. However, so far as the qualitative reaction is concerned, the tissues from all parts of the gastrointestinal tract reacted to stimuli in a normal manner, affording therefore no explanation for the difficulty in swallowing, for the paralysis of the stomach which several writers have described, nor for the obstinate constipation observed in human cases. The explanation must be sought outside of the gastrointestinal tract, either in the central nervous system or in the extrinsic nerves. The addition of pure toxin to the fluid bathing normal tissues had no appreciable effect upon their activity.

Our next examination was as to the effect of the toxin upon the circulatory apparatus when it is injected intravenously in acute experiments. These experiments were carried out on rabbits, cats and dogs. The toxin showed itself to be surprisingly harmless when injected in this way. The injection of 1 or 2 cc doses of pure toxin diluted with a little salt solution had little effect beyond a slight lowering of blood-pressure and some acceleration of the heart, the rate increasing from a normal of 180 to 200 or 210. Records of the contractions of the two chambers of the dog's heart showed a slight weakening especially of the auricles, followed by augmentation. These changes, which will not be discussed at greater length at this time, were greatly exceeded in interest by depression of the vagus nerve, which appeared in varying degrees in different animals. This is evidently the "block" referred to by Dickson in his paper. As the toxin was being injected in small doses, frequently repeated, a gradually lessened reponse on the part of the vagus was noted, until after 15 cc or 20 cc the vagus of a cat or rabbit was almost inactive. In most cases recovery was fairly rapid. In a number of dogs we were unable to demonstrate this action on the vagus, but in one we succeeded in getting a total paralysis from the injection of a small

dose of toxin, also in one or two other dogs and cats and in one cock, in all of which, after normal respiration had ceased, the heart had been kept going under artificial respiration; the vagus was tested and found to be without action on the heart. Numerous variations in vagus response were found during the acute experiments, one of the common ones being that stimulation of the vagus, after the injection of the toxin, was ineffective for perhaps fifteen seconds, as it produced no slowing but would lower the blood-pressure; this was followed by a lessened rate for a few seconds, which might again pass off. It would appear that certain fibers might be depressed, while others would not be attacked to a like extent. We expect to examine into the causes of these changes later.

As will be seen, these acute injection experiments did not throw much light upon the cause of the clinical manifestations of the condition in man. They had, however, furnished the key to the solution of the matter, namely, in the condition of the vagus.

In order to examine into these changes further we changed our method of attack and injected lethal doses of the toxin into animals, and then endeavored to get the animals at the moment of death. We then either examined the reaction of the tissue at that time, or in the larger animals we kept the circulation going under artificial respiration. This brings up an important point, namely, that animals never die of cardiac failure in botulism. It is always failure of the respiration which kills, and if respiration by artificial means be instituted, the animal's life can always be prolonged, as we shall discuss later. Many times in the literature it is stated that in this condition death is due to respiratory or cardiac failure. It would seem doubtful whether in man also death ever occurs in cases of pure botulism from failure of the heart. Some of the more recent writers do say that the heart beats after respiration has stopped, thus confirming our views gained from an extensive experience with animals.

We shall first consider the results obtained in lethal experiments with guinea-pigs. These animals were all examined at the moment that respiration ceased. Of course it goes without saying that many animals were lost, as they died at night or in the early morning hours, when no one was around to make the necessary examina-

tions. With the larger animals, after some experience, we found it possible to make a closer estimate as to the probably duration of life, and so most of them were saved for investigation.

Following the examination of the heart, which we always found to be beating, the condition of the sciatic and phrenic nerves was next investigated. In no case were they found to be normal. In about a quarter of the sciatics examined the response may be said to have been nearly normal—roughly speaking, 80 per cent normal. In another quarter of the cases they might be said to be 25 to 50 per cent normal, while the sciatics in the remaining 50 per cent of the cases were only very feebly active—that is, they could bring out a momentary contraction of the muscle and then cease to act. Even more striking was the difference in duration of response after death. The sciatic of a normal pig, killed by a blow on the head, will remain active for from twenty to twenty-five minutes after death. With the botulinus pigs, on the other hand, even in those sciatics which most closely approached normal, a response was never obtained later than six minutes after death. The muscles in every case seemed to give a normal response. Examination of the phrenics yielded approximately the same results. About 25 per cent were found to be about 80 per cent normal; 25 per cent may be said to be 25 to 50 per cent normal, while the remaining 50 per cent were almost, or totally inactive.

The results obtained on guinea-pigs were confirmed on cats. In 7 animals the sciatics were examined immediately after death. In 1 they were found to give a good response, but the response ceased in five minutes after death, while in normal cats the sciatic was found to give a response from thirty to forty minutes after death. In 4 cats the nerves were only feebly active—just bringing out a response when stimulated and then ceasing to act. In 2 cats the sciatics were entirely inactive.

The phrenics followed in general the same rule. Those in 1 animal gave a good initial response, which failed in five minutes; 2 were feebly active and 4 were totally inactive. The diaphragm responded well to direct stimulation.

In cocks the story was much the same. The sciatics examined were found to be almost inactive—a contraction of the leg muscles

would be brought out by stimulation of the nerve, but it immediately passed into a state of inactivity even with continued stimulation.

An examination into the condition of the motor nerves supplying the neck muscles was next made. Some of these were dissected out in cocks which were kept alive under artificial respiration, and these too were found to be almost inactive—a temporary contraction being all that could be obtained by their stimulation. In one of these botulinus cocks an effort was made to localize more closely the action of the toxin as being upon the nerve ending or upon the receptive substance. The nerve trunk being ineffective and the muscle responding normally, the connecting mechanism must be at fault. Therefore, in one of these cocks in which sciatic stimulation was ineffective, the gastrocnemius was arranged to record its contractions upon a kymograph by attaching the tendon to a writing lever. As will be remembered, Langley[7] showed that in cocks the injection of nicotine will bring out a long-sustained contraction, which in turn is antagonized by curara. These two drugs, acting after the nerve ending has degenerated, must produce their effects by acting upon the receptive substance. Injections of nicotine into a botulinus cock in which the sciatic was paralyzed produced the typical curve which was described by Langley, and it was antagonized by curara. These reactions demonstrated that the receptive substance was probably normal and that the botulinus toxin had exerted its action upon the histological nerve ending. This being true for the cock's leg muscle and sciatic nerve, it would seem to be safe to transfer the point of toxin action also to the phrenic nerve and the peripheral nerves elsewhere.

Also in such a cock the vagus was found to be almost inactive. A heart rate of 162 per minute was slowed to 150 and in another case from 152 to 138 per minute.

In dogs we have not been able to carry the work quite as far as in the other animals, but have found essentially the same condition of impaired activity on the part of the sciatics indicated by lessened response and early failure. On the whole, however, the nerve-ends in dogs seem to be more resistant than those in the smaller animals or in the cock. This is shown during life by the fact that very late in the intoxication, when the respiration is seriously disturbed, the

dog will frequently make rather extensive movements—attempts at standing or changes in position. These movements become more futile, until it seems almost impossible for the animal to raise its head. At times, when the respiration has apparently ceased and the animal has been placed on the table for tracheotomy, it will make efforts at moving and the respiration may be reinstated temporarily.

Discussion. The essential action of the botulinus toxin is therefore a more or less complete paralysis of the motor nerve end-plates in the striated muscles and in the diaphragm. There is also impairment in some other nerve-endings, such as those of the vagus. The full significance of these latter changes we have not arrived at thus far, but hope to report upon them further in a later paper. All the truly characteristic symptoms of botulism, however, can be explained by the peripheral motor paralysis—the paralysis of the extrinsic eye muscles, the ptosis, the difficulty with talking, with protrusion of the tongue and in swallowing. In the latter case the esophagus seems not to be at fault, but the nerves to the pharyngeal muscles, as patients say that if they can get the food past the pharynx it will go down alright. The increasing weakness in the legs, the relaxation of the abdominal wall, the early change in the respiration, due to the paralysis of the diaphragm, all have the same origin, and the final failure of the respiration is due to the failure of the nerve-endings in the respiratory muscles. It is a death due to peripheral causes and not to failure of the respiratory center.

Late in poisoning, when the movements of the ribs are becoming weaker and weaker, there is just enough activity in the nerve-ends to transmit the impulses to the respiratory muscles and additional demands will result in death. This was well illustrated in one of the cats which was maintaining a respiration which was just adequate to its needs. One of us placed his hand lightly on the chest to get the heart rate, but even this slight pressure stopped the respiration and the animal straightened out as though dying—as indeed it was. A tracheal tube was rapidly inserted and artificial respiration instituted and maintained for three hours. At the end of that time wishing to examine the condition of the sciatics, the artificial respiration was discontinued, but to our surprise the cat, after a few moments, started to breathe voluntarily and kept up an adequate

respiratory movement until it was killed to make the examination mentioned.

The circulatory apparatus in these animals is apparently normal. In one cat, which had ceased to breathe and which had had artificial respiration for three hours, a carotid cannula was inserted and the blood-pressure taken. It was found to be 170 mm. Hg. Stimulation of a sensory nerve gave a good reaction, increasing the blood-pressure to 200 mm. Hg.

In dogs too, after hours of artificial respiration, blood-pressures of over 100 mm. Hg have been found, thus making us think, as we said earlier, that in uncomplicated cases of botulism the cause of death is always failure of the respiration and not of the heart.

Fate of the Toxin in the Body. We have made a few observations upon the fate of the toxin in the body. In some of the dogs which have been poisoned with the toxin we have withdrawn urine with a syringe from the bladder and have injected it intraperitoneally into guinea-pigs in doses as large as 5 or 10 cc, but with no ill effects.

In the same way we have withdrawn blood from the carotid of a dog which had been kept alive for twenty-four hours by artificial respiration, and have injected this into guinea-pigs, and have produced typical symptoms of botulism in the pig. The toxin then apparently is not excreted in the urine but may be found in the blood of a dog seventy-two hours after it has been injected intraperitoneally and twenty-four hours after the animal's respiration has ceased.

Treatment. These findings have led us to formulate certain ideas as to the best method of treatment of the poisoning in man. The first method should, of course, be directed toward artificial respiration. We have tried this in dogs with a certain degree of success. We have kept a dog alive for thirty hours and others for shorter periods of time—the shortest time being six hours. There are, of course, difficulties in the way in animals and doubtless in man. The question of dose of toxin is of course important. The idea is to tide persons over until they can destroy the poison. If there is an overwhelming dose, as in some of our animals, it may not be possible to do this. On the other hand, in certain cases the dose of toxin ingested may not be great, and the question of a few hours'

extra may prove life-saving. The difficulty we have had thus far, and which we hope to obviate in the future, is that with our method of carrying on artificial respiration with a bellows we wash out the animal's CO_2 and they die of CO_2 poverty and not of botulism. Some time before death all reflexes disappear, the heart accelerates and at postmortem it is found in complete systole. The condition coincides perfectly with that described years ago by Yandell Henderson[8] and produced by him in animals by excessive respiration. In our dogs the production of CO_2 is doubtless at a minimum, as they are lying quietly, and in many cases they are asleep from small doses of chloretone which have been given to keep them from moving. On the other hand, the constant ventilation of the lungs with fresh air lowers the CO_2 until a point is reached below which life is impossible. We hope in further experiments to be able to overcome this difficulty. We believe that in human beings the difficulty would probably not be so great, as personal coöperation would be possible and an anesthetic not necessary. It is true that there is no machine which is satisfactory for the maintenance of artificial respiration in man; but the ordinary bellows connected with a tracheal cannula would suffice in the case of an emergency.

The question as to drug treatment naturally arises. It is clear, from what has been said earlier in this paper, that we have to do with a curara action, using this term in rather a loose sense and not distinguishing between nerve-ending and receptive substance. For curara it is well known that the best antagonist is physostigmine. Animals which have been paralyzed with curara can be recovered at times by physostigmine.

We have tried the effect of this alkaloid in only a few animals, but up to the present time have not worked out a satisfactory dosage, and in addition the dogs we have been able to reach at just the right moment of cessation of the respiration we have utilized to study the effect of artificial respiration and the condition of the circulatory system. In the few animals in which we have been able to try it we have seen improvement. Cocks which have limber neck and have seemed to be totally paralyzed have, after a small dose of physostigmine, made efforts at standing and have shown more movement in the neck. All animals in which we have tried the

alkaloid have responded with increased movements and a general improvement in symptoms. Our main difficulty up to this time has been with the question of dosage. We hope that with more material and a careful regulation of dose to be able to report further progress at a later time. It is very important that the dosage in man should be carefully regulated until the reaction of the patient has been seen. This would apply especially to the increase of secretions along the respiratory tract, which in case they became excessive might be embarrassing.

As to the effect upon the skeletal muscles, the action of physostigmine is well known. In excessive doses it is doubtless true that those muscles the nerve-ends of which still retain some activity will react more than those which are more or less completely paralyzed. We have seen this in dogs with excessive dosage, in which case convulsive movements might appear in the mouth and neck muscles, while the muscles of the hindlegs were totally inactive.

An interesting result of a large dose of physostigmine was seen in one dog which, as a result of botulism, was under artificial respiration, as its normal breathing had failed and there was almost total paralysis of the entire animal. Four milligrams of physostigmine were injected into the circulation, and in a short time the animal had a generalized convulsion lasting several minutes. This was followed by failure of the heart and death.

In this brief discussion of the treatment of cases of human botulism we of course have not gone into the use of the specific antitoxin nor into the general care of the patient, but merely into those two lines of treatment which are suggested by our experimental work. We would have liked to have been able to have reported more conclusive results upon the effect of these two therapeutic measures, especially as to the effect of physostigmine, but while continuing our experiments are offering them as suggestions, as doubtless cases of botulism will occur in isolated areas as in the past, and opportunity will be found of testing the value of the measures. Certainly nothing in this newer knowledge of the pathological physiology of the condition would give any grounds for thinking that there is any value to be expected from the use of any one of the numerous drugs which have been suggested in recent reviews of the therapeutics of the intoxication.

SUMMARY. There is in botulism a partial paralysis of the endings of the motor nerves going to the voluntary muscles. In some cases this curara-like action is almost complete, as in the case of the nerves supplying the neck muscles of chickens. This action will explain all of the characteristic symptoms of botulism which are motor in origin. The involvement of the phrenics explains the early paralysis of the diaphragm. The effect of the toxin upon the nerves to the respiratory muscles is responsible for the gradually increasing weakness of the respiration and for its final failure which is responsible for death under this form of poisoning.

The involuntary muscle of the esophagus, stomach and intestine acts in a normal manner to epinephrine, physostigmine and other peripherally acting drugs, indicating that the symptoms such as difficulty in swallowing, constipation, etc., are probably not due to an action of the toxin upon structures located in the gastro-intestinal wall. The vagus nerve is also affected, as it largely loses its control over the heart rate, probably accounting for the acceleration of the heart described in certain of the cases of human botulism.

The toxin is apparently not excreted in the urine but may be demonstrated in the blood long after it has been injected.

On the basis of the experimental work it is recommended that in cases of human botulism when the respiration shows signs of failure that artificial respiration should be instituted—if necessary by means of bellows and a tracheal cannula. In dogs this procedure has given promise of success. The careful adminstration of physostigmine is also recommended.

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A NEW CLASSIFICATION OF MYCETISMUS (MUSHROOM POISONING)

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During the past few years our ideas as to the number of mushrooms which may be poisonous to man on ingestion have been greatly modified. This changed opinion has resulted primarily from the numerous investigations upon animals which have been carried out in several different laboratories and which have shown that the well-known poisonous principles of fungi are much more widely distributed than was originally believed. Furthermore, the food conditions in Central Europe have been of such a character for seven or eight years that people were forced to utilize almost every variety of plant that seemed likely to have nutritious properties. Observers who have returned from Germany and Austria, for instance, have reported that during and immediately after the war the woods and fields were searched so thoroughly for edible fungi that they were practically denuded of plants of this type. In consequence the number of cases of mushroom-poisoning increased very markedly. The late Prof. Kobert, just before his death, reported one hundred instances of *Amanita muscaria* poisoning in a district where previously "muscaria" intoxication was almost unknown.

Numerous clinical reports on mushroom-poisoning have now appeared in the German medical literature accompanied by very careful pathological examinations in the fatal cases, the lesions being studied by modern methods. The pathological investigations of Fraenkel, Herzog, Schmidt and a number of other pathologists have filled a large gap in our knowledge of mycetismus and have greatly clarified our ideas.

At the present time we know that there are from seventy to eighty different species of fungi which may be poisonous to man. It is manifestly impossible for the clinician to be familiar with more than a few of these species. Furthermore, in the majority of cases specimens of the mushrooms which have been eaten are not available for examination, and the patient's statements are often quite confused and inaccurate. We must therefore depend in our treatment and prognosis upon the symptomatology of the cases. Since the symptoms depend on the active principles of the plants, the question rises whether we cannot classify the cases of mushroom-intoxication on the basis of symptoms by some method which will be in harmony with our pharmacological and pathological knowledge. If this can be accomplished it is possible that the treatment of mushroom-intoxication can be made more effective than it is at the present time. The wide prevalence of serious accidents from mushrooms in America is ample justification for such an attempt.

The only classification of mushroom-intoxication which has been generally accepted is that of Huseman, which was established over forty years ago. Huseman divided mycetismus into three types, intestinal, choleriform and cerebral. The intestinal mycetismus was due to an acute gastro-intestinal inflammation produced by certain species of Boletus, Russula and Lactarius, which harbored active principles injurious to the alimentary mucosa. The choleriform mycetismus showed a similar gastro-intestinal disturbance, violent vomiting and diarrhea, but was accompanied by severe cramp-like abdominal pains from which the patients collapsed, dying in delirium and coma. This type of mycetismus was traced by Huseman to *Amanita phalloides* and *Helvella esculenta*. Finally, the cerebral form with symptoms, arising from excitation of the nerve centers, was traced by Huseman to *Amanita muscaria* and *Amanita pantherina*, but was attributed to an atropin-like principle in these plants and not to muscarin.

Our more accurate knowledge of poisonous mushrooms indicates that Huseman's classification is only partially correct. I suggest therefore, the following classification as more in accord with modern conceptions:

1. Mycetismus Gastro-intestinalis. In this type the symptoms are nausea, vomiting and diarrhea. They may vary greatly in severity from mild vomiting or simple painless catharsis to violent retching and purging, accompanied by severe cramps in the abdomen. The symptoms terminate rapidly and usually spontaneously, and the patients are restored to health in a day or two. There are practically no fatalities except in debilitated individuals. The principal fungi responsible for this type of poisoning are *Russula emetica, Boletus satanas, Boletus miniato-olivacius, Lactarius torminosus, Entoloma lividum* and *Lepiota morgani.*

2. Mycetismus Choleriformis. In this type gastro-intestinal symptoms predominate at the outset, appearing ten to fifteen hours after the fungi are eaten. They are very violent, cramp-like in character, and accompanied by vomiting and purging. After a period of remission the attacks of abdominal pain recur and are often so severe as to produce a Hippocratic facies. The loss of strength and weight is rapid and in some cases the patients may die in from two to five days. The mortality is high, at least half the patients succumbing to the poisoning. Especial attention has recently been directed to the kidney involvement, and we now recognize that the kidney is badly damaged. Casts of all varieties and albumin appear in the urine, and the kidney function is impaired. In the treatment but little can be accomplished beyond the relief of the intense suffering and the administration of remedies to relieve the kidney complications. The stomach and intestines should be washed out thoroughly and repeatedly and digitalis and strychnia employed when the heart action is weakened.

The lesions in this type of mycetismus are degenerative in character, localized in the liver, kidney and heart muscle. Recent pathological studies indicate that there is considerable attempt at repair of the injured tissues, especially in the liver. The possibility of recovering, even in the most severe cases, must not be lost sight of, and every attempt made to prolong the life of the patient until the action of the poison has worn off.

This form of mycetismus is due to the white *Amanita phalloides* and to several closely related plants. Poisoning from *Pholiota*

autumnalis and *Hygrophorus conicus*, in which the symptoms are much the same, may be placed provisionally in this group.

3. Mycetismus Nervosus. Here violent gastro-intestinal symptoms appear early, often two or three hours after the fungi are eaten. These symptoms are accompanied by contracted pupils, profuse perspiration and salivation, convulsive movements of various muscles and often violent convulsions of almost the entire body. The patients develop delirium, hallucinations and die in coma, usually from an acutely dilated heart. In this form of mycetismus we may place all the cases of poisoning from fungi containing muscarin, which will produced experimentally in animals practically all the symptoms seen in man. The poison has a selective action on the nerve terminals.

The treatment of this form of mushroom-poisoning is more satisfactory than in any other form. Atropin is almost a complete physiological antidote for muscarin. It should be employed early and in large doses, both subcutaneously and intravenously. In cases with acute stoppage of the heart in diastole the direct injection of the drug into the heart muscle should be considered. After subsidence of the acute symptoms from the muscarin in the plants the patients convalesce rapidly and are restored to complete health in a few days, no permanent lesions of the organs being produced.

The principal mushrooms which can produce this form of poisoning are those containing muscarin in large quantity: *Amanita muscaria Amanita pantherina*, various inocybes like *Inocybe infelix* and *Inocybe infida*, and *Clitocybe illudens*.

Fungi containing small quantities of muscarin, like *Clitocybe sudorifica*, while not so dangerous as others, should be put in the same category, since the symptoms are practically the same, only milder.

4. Mycetismus Sanguinareus. This rare variety of mushroom-poisoning is a true hemolytic intoxication resulting from ingestion of plants which contain substances acting directly on the red blood corpuscles. The patients have a transient hemoglobinuria accompanied by vague abdominal distress, and in four or five days develop a mild jaundice which lasts a considerable time. The prognosis is usually good, but several deaths are on record, both in Europe and

in America. At autopsy there is evidence of extensive destruction of the red blood corpuscles, a widespread pigmentation of liver, spleen and kidneys. The logical treatment for this kind of mushroom-poisoning is tranfusion of blood from a homologous donor. Apparently, however, this has not been tried. The only mushroom producing hemolytic intoxication is *Helvella esculenta* (*Gyromytra esculenta*), which contains a heat-resistant hemolytic poison, *Helvellic acid*.

5. Mycetismus Cerebralis. Here the patients show peculiar cerebral symptoms four or five hours after the fungi are eaten. They are greatly exhilarated, laugh immoderately on slight occasion, develop a staggering gait and show peculiar disturbances of vision. The symptoms are transient, the patients being restored to health in twenty-four to forty-eight hours, except for a peculiar sensation which they describe as a feeling "as if they were walking on air." This subjective sensation may last several days.

The plants responsible for this peculiar poisoning are *Panaeolus papilionaceus* and *Panaeolus campanulatus*. They are of interest to us chiefly in that they grow on lawns together with the edible mushroom, *Agaricus campanulatus*, and also rarely in beds for the artificial propagation of this species.

CHYLOUS AND CHYLIFORM ASCITES[1]

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Milky ascitic fluids are usually called chylous, chyliform and pseudochylous, according to their source in the body. If they are known to come from the chyliferous sytem they are called chylous. If they are thought to come from elsewhere they are called chyliform or pseudochylous without distinction between the terms. It is seldom that the source of such milky fluids can be determined by examination of the patient; therefore, examination of the fluid obtained from the patient has been expected to reveal the source and the cause of the effusion. Frequently these fluids are indeterminate as to their properties and constituents, so that little information is forthcoming. This want of information has inspired numerous efforts at classification of body fluids and has bred the confusion of terms. This investigation strikes at the root of the matter as it now stands and aims to show that the differences whereby chylous fluids are to be distinguished from other milky fluids do not exist. It is shown in this investigation that turbidity is in all instances due to fat and that therefore other criteria must be found to evaluate these unusal fluids as diagnostic signs.

Now the accepted classification is based upon the fact that the chylous fluids contain coarse fat particles and can be "shaken out," while pseudochylous and chyliform fluids when shaken with fat solvents (principally ether and petroleum ether) do not clear and no fat is extracted; and, further, that when dried residues of the same are extracted only very small amounts of the fat are found, not sufficient to be the cause of turbidity. Furthermore, when

[1] From the Department of Medicine, Western Reserve University, Lakeside Hospital, Cleveland, Ohio.

protein is isolated from these turbid fluids, as by salting out, by heat or by acid coagulation, the turbidity has been dispelled. Thus it was obvious that with little or no fat present, protein should be the cause of milkiness. But I have found that finely divided fat—and by fat I mean the neutral fats, fatty acids, lecithin and cholesterin, and all the lipoid substances common to blood—does cause the turbidity without any necessary relation with any protein. This conclusion was based on examination of fluids from eight different patients, first by chemical assay, but mainly by physical and physicochemical methods employed to explain the nature of the turbidity. In confirmation of the fact that fat alone is responsible for milky fluids, I synthesized milky fluids from fat which satisfied entirely all requirements of the problem. I was able to produce these fluids also in dogs by tying the thoracic duct in the neck and then by operation producing a thoracic duct fistula into the pleural cavity. From this cavity we aspirated fluids which, after removal of the grosser fat, corresponded in every respect to the classical chyliform fluid.

Similar fluids were made by suspending cod-liver oil in a coarse emulsion in a watery solution of protein and salt to which had been added alkali to a Ph of 7.4, the whole then being repeatedly run through a homogenizer at a pressure of about 800 pounds. This oil-protein-water mixture contained many coarse particles, but after removal of these there remained a suspension of ultramicroscopical particles which could not be shaken out with ether but were precipitated by all the devices that would precipitate protein. Twenty mg. per 100 cc of cod-liver oil will produce a very satisfactory fluid, whereas natural pseudochylous fluids usually contain from 20 to 100 mg. per 1 cc of fat. Identical fluids were synthesized by cod-liver oil, water and alkali, which behaved exactly the same way, showing that no protein is essential.

To test the matter further, another fluid was made of a non-saponifiable fat—namely, liquid petrolatum suspended in distilled water. In this about 10 mg. per 100 cc of oil remained in permanent suspension, and this in the absence of any protein or any electrolyte. The fluid was milky, resisted clearing by shaking, but was cleared by any device that would remove protein. It is thus

apparent that fat, if finely enough divided, can remain in a permanent suspension in water, resisting the clearing effect of ether but precipitated by the usual manipulations that removed protein. All these attributes can be explained as phenomena of surface tension and electric charge, for I can show that colloid fat and protein in alkaline media have the same electric charge but different isoelectric points.

Inasmuch as lecithin has been the principal contender for the role of turbidity, I attempted to make lecithin-globulin suspensions and lecithin suspensions alone. These can be made perfectly satisfactorily in an acid medium or absolutely neutral, but the moment the alkali titer goes a few points above the neutral the entire suspension of lecithin is saponified and the suspension clears.

From this much experimentation it is quite apparent that finely emulsified fat can of itself alone present all the peculiar behavior which is commonly ascribed to suspensions of protein.

The actual pathological material examined in this investigation was from 8 different patients as follows: 1 with tumor of the mediastinum; 1 with chronic nephritis; 1 with chronic fibrous peritonitis and pleurisy (cause unknown); 1 with arteriovenous aneurysm; 1 with thoracic aneurysm; 1 with anasarca complicating typhoid fever. Six of these specimens were examined by very searching methods herein mentioned. The other 2 were not so thoroughly examined and were studied before this investigation began.

All of these fluids were assayed chemically by the usual methods and could be classified as chylous or chyliform. It was seen in all of the specimens that after prolonged and vigorous centrifuging a more or less heavy layer of cream could be removed, leavingan underlying fluid typically chyliform. It is with this substance that we are principally concerned.

The methods of examination were: filtration; sedimentation; heat coagulation; salting out; mutual precipitation; extraction; freezing; peptization; electrolysis; dialysis. Of these methods of examination only those of more decisive results will be discussed; for reasons of brevity the others will be but mentioned.[1]

[1] The reader is referred to Arch. Int. Med., July, 1923, for a complete discussion of these methods.

Peptization was employed with the expectation that if turbidity of chyliform fluids were due to suspension of protein, turbidity would disappear when these proteins were all split down to the form of peptones. Various forms of pepsin and pancreatin were used, but no change was apparent even when the peptization was shown to be complete and no recognizable protein other than peptone was present.

By electrolysis it was shown that in alkaline solutions suspended fat and protein migrate to the positive (anode) electrode, but in acid media the migration of suspended protein is reversed while that of suspended fat remains unchanged. By electrolyzing in cells of proper construction at a PH very near the isoelectric point of the protein, a separation of suspended fat from suspended protein is accomplished. On examining the content of the cells, protein is found in one and is clear, while fat is in another and turbid. No complete separation was accomplished, but enough to demonstrate that turbidity resides with the fat.

Extraction and clearing were never accomplished by any device where the fat solvent was not miscible with the water of the suspending medium. This at first strongly suggests the absence of suspended fat, but when mixtures of equal parts of alcohol and ether were shaken with the chyliform fluids they were all promptly and entirely cleared. This procedure must be done rapidly and with care, to avoid saturation with alcohol sufficient to coagulate protein, for then a new turbidity appears. If it is properly done they all shake out beautifully, showing that fat is the substance causing turbidity.

Therefore, as suspended fat and fat alone is the cause of turbidity in all these fluids, I propose that the misleading terms pseudochylous and chyliform be discarded.

THE ETIOLOGICAL RELATION OF ACHYLIA GASTRICA TO COMBINED SCLEROSIS OF THE SPINAL CORD

WITH REMARKS ON THE RELIEF OF SYMPTOMS FOLLOWING ADEQUATE HYDROCHLORIC ACID THERAPY

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In a recent clinical study of 451 patients with achylia gastrica there were 29 individuals with definite evidence of combined sclerosis of the spinal cord. Of these 29 patients, 14 had pernicious anemia, 1 had pellagra, in 7 the observations were unsatisfactory or incomplete, leaving 7 patients that form the basis of this article.

I. Summary of the Cases. These 7 patients with combined sclerosis of the spinal cord all received complete clinical and laboratory studies. The gastric analyses were made by the fractional method, one examination being made in Cases IV, VI and VII, two examinations in Cases I, II and V, and 7 gastric analyses were made in Case III. Blood counts were made in all cases, together with a study of the stained smears, and showed no evidence of pernicious anemia except the late developments in Case VII. The Wassermann reaction on the blood serum was negative in all cases and the spinal fluid was examined and found normal in Cases II, III and V. The blood sugar was examined and found normal in Cases III, V and VI and the nitrogen content of the blood was found normal in Cases III, V, VI and VII.

Foci of chronic infection were sought for in all cases; in Case VII none could be found; Case III had infected tonsils, which were removed; Case II had a mild prostatitis, which cleared up on treat-

ment; Cases I, II and III showed apical abscesses about certain teeth on *x*-ray examination, and these teeth were extracted; Case IV showed marked pyorrhea alveolaris; Case V had had all of his remaining teeth extracted two months before the onset of his paresthesias, and he stated that several of these teeth were abscessed; Case VI had lost all his teeth except four, and these showed extensive pyorrhea. Cases III and VI showed moderate arterial hypertension. In the 5 remaining cases the blood-pressure was normal.

Treatment in each case consisted in the removal of such foci of infection as could be found, and the regular and persistent administration of one teaspoonful of the official dilute hydrochloric acid with each meal. The acid was given in 6 or 8 ounces of water, lemonade, orangeade, iced tea or, preferably, buttermilk. The results of treatment are particularly interesting in that Case III is subjectively cured, Cases I and V are apparently well and Case VI is greatly improved. Case IV discontinued his treatment and later wrote that he was unimproved. Case VII is growing progressively worse, but it is learned that he took the hydrochloric acid in inadequate amounts and later discontinued it. Case II took his hydrochloric acid regularly but died two and a half years after his treatment was started of progressive spinal-cord symptoms. A brief abstract of the histories of these 7 cases follow:

II. Abstract of the Case Histories

Case I.—Mrs. M., married, aged fifty-one years, was seen May 21, 1918, complaining of a burning, creeping sensation in the feet and legs of six months' duration. These paresthesias were worse at night and kept her from sleeping. Had had no indigestion since her gall-bladder was removed in 1913, except for a morning diarrhea for the past six years. Her tongue was clean but not bald.

Patient returned for observation January 4, 1919. She had taken the hydrochloric acid regularly until November, 1918, and the paresthesias in the feet improved; she then stopped the acid and the burning in the feet returned. She then resumed the acid but the burning sensation in the feet persisted for some time. Her diarrhea stopped when she was first put on the hydrochloric acid and her bowels were regular until she stopped the acid, when they became loose again.

Patient was last heard from on February 14, 1923, when she wrote, in response to an inquiry addressed to her home in another state, as follows:

"I have taken the hydrochloric acid regularly, only leaving it off occasionally to watch the effect. I find that my feet burn if I leave it off more than two days. I still take the dose prescribed by you. Have not had a doctor since I saw you, and do not know if I am anemic, but I seem to be well."

Case II.—Mr. D., married, aged sixty-five years, a retired farmer, was first seen March 11, 1919, complaining of numbness in hands and feet of four months' duration. His past health had been excellent, with no history of acute infections, except an attack of gonorrhea at the age of twenty years. Gave a history of sciatica ten years previously, with gradual recovery and no recurrence. Appetite was good and he gave no history of digestive disturbance except occasional slight diarrhea and, more recently, some flatulence. Had used tobacco and liquor in moderation in the past but not in recent years. No loss of weight. His first symptom was numbness and tingling in the fingers and toes on the left side, with similar involvement, a few days later, on the right side. A little later he noticed numbness on the inner aspects of both thighs and then over the abdomen up to the rib margins. Had had no darting pains, no muscular weakness, no difficulty in walking in the dark and no incontinence of the sphincters. Smooth objects, like apples, felt rough to his fingers. Had observed no objective change in the extremities. The tongue was clean and distinctly red about the margins and tip.

He was next seen in October, 1919, when he stated that his numbness was worse and affected the hands, forearms, feet, legs and hips. Had difficulty in picking up small objects and in writing. (Constantly rubbed the palmar surface of the thumb of each hand against the palmar surface of the fingers.) Was a little unsteady on his feet, but said he had no difficulty in walking. Had no pain or stiffness in his back. Had taken his hydrochloric acid regularly in teaspoonful doses with his meals. Said that he suffered with sore tongue for years before taking this acid, but not since. Had had no further diarrhea. Digestion was good. Had no urinary disturbances. The tongue was red and clean.

Patient was next seen in January, 1920. Had lost 9 pounds since March, 1919. His general condition appeared to be unchanged. The neurological findings indicated that the trouble had been progressive.

In May, 1921, I saw the patient for the last time at his home in a distant part of the state, and he then showed a flaccid paraplegia with marked ataxia, absent deep reflexes and involvement of the sphincters. He died in October, 1921. For three weeks prior to his death he had difficulty in swallowing and retention of urine. His family physician reported that at no time did he present any appearance of pernicious anemia, and that several blood counts made during the last few months of his life showed

no reduction in either the red-cell count or in the hemoglobin. It was understood that patient took full doses of hydrochloric acid during practically the whole period of his illness.

Case III.—Mrs. F., aged forty-two years, first consulted me on November 15, 1919, complaining of a sensation of numbness which began in the feet in February, 1919, and then gradually extended up the legs and trunk to the waistline. A little later she developed numbness in the hands and arms, extending up to the elbows. She said that the soles of her feet felt as if she were walking on something very stiff, not like cotton. Said she had difficulty in walking, could not manage her feet well, was inclined to catch hold of things when she walked and that she fell easily. Had difficulty in picking up small objects and in fastening her clothes and often dropped things. Said she had no tingling and no loss of touch sensation. About three years previously developed a sore mouth and since then the tongue had been red and inflamed.

Her past history showed that she had malaria at seventeen, diphtheria at twenty-one, attacks of tonsillitis, but none in the past eight years and influenza in 1918. Appendix and one ovary were removed in 1904. Had had no indigestion except flatulence. The bowels were constipated. Had acute cystitis with hematuria in June, 1919. At that time was found to have increased blood-pressure. The tongue was moist, red and clean.

Patient was again seen in May, 1920, October, 1920, June, 1921, June, 1922, and March, 1923. By October, 1920, the numbness in the extremities had disappeared except for slight paresthesia in both feet, and she had no further stomatitis. Since that time patient had considered herself entirely well. When last seen in March, 1923, she said she had no numbness at all except occasionally when tired she might notice a feeling of sleepiness or heaviness in her feet and legs. Her appetite was splendid and she had no indigestion of any kind. She was again completely examined and her seventh gastric analysis showed a complete achylia. It was interesting to note that, in spite of the disappearance of subjective symptoms, the physical signs persisted. All of the deep reflexes were exaggerated, there was an exhaustible ankle clonus and sensation to touch was greatly impaired from the feet up to a point midway from the ankle to the knee on each side. She had taken her hydrochloric acid regularly since 1919 and was advised to continue it.

Case IV.—Mr. M., married, farmer, aged sixty years, was seen on April 13, 1920, complaining of stomach trouble and a crawling sensation in his legs. His past history included malaria in 1910, grippe in 1905 and rather frequent sore throat. Otherwise it was unimportant. Had used tobacco freely, very little liquor. Was 12 pounds below his usual weight.

His present illness dated back one year previously, when he developed pain in the abdomen and paresthesias in the extremities. The epigastric pain was never severe, usually occurred two or three hours after meals, and he was constipated. He had had no nausea, vomiting or flatulence and gave no history of acute pain or colics. The paresthesias were described as a peculiar crawling sensation in the legs, with a burning in the feet and ankles. His tongue was clean. In response to an inquiry, patient wrote, under date of March 14, 1923, from his home in the country, that he had "not been able" to take the acid, that he continued to suffer with the burning sensation in his legs and that his digestion was poor.

Case V.—Mr. M., single, lawyer, aged sixty-one years, was seen on November 28, 1921, complaining of numbness and loss of control of legs and hands. He used to have a good deal of indigestion, and beginning in 1891 he had diarrhea with undigested food in his stools for two years. (Described a rather typical gastrogenous diarrhea.) His digestion then improved until 1914, when he again developed diarrhea and weakness. Gastric analysis at that time showed a complete achylia. (This fact was confirmed by communication with the physician who examined him at that time.) He was given small doses of hydrochloric acid but did not take it very regularly. His appendix was removed in 1915 and since that time his bowels had been regular, and he regarded his digestion as very good. His past history was otherwise unimportant. He smoked and drank in a moderate way.

In March, 1921, the patient has some rheumatic pains in the lower legs. All his remaining teeth were extracted in August, 1921. He stated that several of these were abscessed. Early in October, 1921, he noticed a numbness and peculiar feeling in the left great toe. This numbness soon spread to the other toes and to the foot, and soon started in the same way in the right foot, gradually spread up both legs to the groins, and he then developed a tight feeling about the trunk as if a cord were tied around the waist. Shortly after the onset of the paresthesias in the feet the same numbness developed in the fingers of both sides and then spread over the hands. He complained that he did not have proper control of the arms and legs, and had difficulty in writing and in walking. Had had no headache, vertigo or unconscious attacks. No sore mouth. He wore his shoes unlaced because of his paresthesias, and was constantly rubbing his thumb and fingers together (as did Case II) but had no tremors or pill-rolling motion. The tongue was clean but not bald. He was again seen on December 28, 1921. His weight was the same and his general condition was unchanged except that he said the feeling of tightness around his waist had risen a little higher on his trunk and was then noticed around the lower part of the chest.

Patient returned for examination, by request, in April, 1923. He stated that he regarded himself as well and was actively engaged in his law practice. He said that the greatest improvement had occurred in his hands, in which the numbness had practically disappeared. The girdle sensation had also gone, together with the constricted feeling across the hips and lower abdomen. He had no difficulty in writing or in walking. He continued to be conscious of some numbness in his feet and legs. He had taken the hydrochloric acid regularly. His appetite was good, he had no indigestion or sore mouth and his bowels were regular. Examination showed that the physical signs persisted in the lower extremities, with absent deep reflexes and definite loss of sensation to touch, with diminished pain sense, especially over the inner aspect of the legs. Gastric analysis was repeated at this time and showed free hydrochloric acid absent at the end of thirty, forty-five and sixty minutes. Blood count showed red cells, 4,216,000; hemoglobin, 85 per cent; differential leukocyte count and morphological picture normal.

Case VI.—Mr. S., married, farmer, aged seventy-one years, was seen on June 28, 1922, complaining of intense burning in the feet of four months' duration. His past history showed that his general health had been excellent; had had some indigestion when a younger man, characterized by sour stomach, but had had no digestive disturbance in the past twenty years. Bowels had always been regular. Had used tobacco but no liquor. Was underweight about 10 pounds. The latter part of February, 1922, he suddenly developed a burning sensation on the soles of both feet without any redness or swelling. Then gradually developed numbness in both legs, with a sensation as if water were dripping on them, and some difficulty in walking. Had also developed burning in the ends of the fingers and some burning spots on the face. The burning in the feet was very distressing, and at first was constant day and night, but after taking some medicine from his home physician he had been able to secure some sleep at night. Said that his hands felt drawn and cramped. The tongue was lightly coated.

On March 16, 1923, patient's physician wrote as follows: "Mr. S. asked me to reply to your letter and to say that he weighs 15 pounds more than he has for thirty years; that he has taken his hydrochloric acid every day since he saw you, except eight days; that his feet do not burn at night but do burn some in the daytime; that he eats anything and as much as he wants." The physician added that the patient looked a good deal better and was not anemic.

Case VII.—Dr. X., married, physician, aged sixty-four years, was first seen by a colleague on June 5, 1922, and the case has since then been fol-

lowed by both of us. Patient's past health had always been very good. He had had influenza in 1918 and again in 1921; otherwise had had no illnesses and no acute infections since childhood. He had been a moderate smoker, but had never used liquor. He dated the onset of his present illness to an attack of influenza in October, 1921, although he had not felt well since December, 1920, when, after some exertion, he had a brief attack of dizziness, confusion and a feeling of prostration. About October, 1921, he began to suffer from distressing paresthesias with numbness in the feet, legs and hands. He became nervous, anxious and irritable, and had some dizziness. He developed difficulty in using his fingers for finer movements and his gait had become uncertain. He had had no headache, or convulsive attacks, no disturbances of the special senses, and he gave no history of digestive disturbances or any loss of weight. Gastric analysis was made because of the paresthesias and evident cord changes, and showed free HCl absent at thirty and forty-five minutes after an Ewald test breakfast, after which time the stomach was found empty.

Patient was seen again on December 16, 1922. He had deteriorated mentally, was restless and irritable, and unable to work. Showed increasing signs of involvement of the pyramidal tracts and complained very much of his paresthesias. The blood count at this time, confirmed by a second count the next day, showed a normal morphological appearance and leukocyte count, but the color index was high, the red cells numbering 2,576,000 and the hemoglobin 70 per cent.

On April 9, 1923, it was reported that the paresthesias persisted and involved the hands, feet, legs and abdomen. He continually rubbed the thumb against the fingers. Strength was fairly good, but he showed a rather pronounced spastic paraplegia. There was no ataxia, no tremors and no cranial nerve palsies. Last year he took 30 drops of dilute hydrochloric acid with meals for several months, after which he discontinued it. Blood count today showed red cells, 2,768,000; hemoglobin, 73 per cent; differential leukocyte count normal, no nucleated red cells, slight anisocytosis, no poikilocytosis and no basophilic degeneration.

III. The Pathology and Symptomatology of Combined Sclerosis of the Spinal Cord. Combined sclerosis of the spinal cord is characterized anatomically by degenerative lesions in the posterior and lateral columns, and the affected areas are unlike those occurring in any other disease in that no neurogliar increase follows the degeneration. Collier,[1] in his recent monograph, states that the clinical features of subacute combined degeneration of the spinal cord are usually strikingly distinct in that subjective sensations, such as tingling, numbness and burning, occurring

usually at the periphery of the extremities, are early, obtrusive and persistent symptoms, and are accompanied or followed by the development of a paraplegia which may be of a spastic type, or of a flaccid and ataxic type, or of a mixed type, according to the degree of affection of the lateral and of the posterior columns in each case. The deep reflexes are present, exaggerated or absent, according to the relative affection of these columns. Loss of sensibility of peculiar distribution occur, which has a "glove-and-stocking" distribution upon the extremities and a segmental distribution upon the trunk. In the late stages of the malady the paraplegia tends to become complete and of the flaccid type, with loss of the deep reflexes. It is a disease of adult life, most of the cases occurring in the fifth, sixth and seventh decades. The sexes are equally affected, heredity is not a factor, and syphilis plays no part in the etiology.

IV. The Relation of Pernicious Anemia to Combined Sclerosis of the Spinal Cord. The intimate relation of pernicious anemia to combined sclerosis of the spinal cord has been emphasized by many writers,[2] and the earlier authors believed that the degeneration in the nervous system was the result of vascular changes consequent upon the anemia. This point is negatived, as pointed out by Collier, by the facts that some cases of combined spinal sclerosis progress to a fatal issue without any evidence of anemia, and that in others the nervous manifestations may become severe long before any anemia is evident. Collier concludes that certain experimental evidence as well as the clinical and pathological features of the disease suggest that the anemia and the degeneration of the nervous system are not dependent the one upon the other, but that they are the concomitant but not necessarily synchronous results of one and the same cause.

V. The Association of Achylia Gastrica with Pernicious Anemia. The almost invariable association of achylia gastrica with pernicious anemia has been recognized for many years. Among the more recent reports is that of Levine and Ladd,[3] who report an absence of free hydrochloric acid in the gastric contents of 104 out of 107 patients suffering from pernicious anemia Here, again, the older writers were inclined to attribute the achlorhydria to the

anemia, and the view continues to be put forth that pernicious anemia causes gastric anacidity. That such an opinion is erroneous would seem, however, to be abundantly proven by the accumulated reports in the literature of cases in which it has been shown that persistent achylia gastrica precedes by months or years the onset of pernicious anemia; also, by the fact that the achlorhydria persists throughout periods of remission in pernicious anemia; and, again, by the fact that there is no constant curve of gastric secretion in other forms of severe anemia, and that the most pronounced secondary anemias do not show achlorhydria as a rule. Finally, and this seems very conclusive, pernicious anemia has subsequently developed in certain patients following the artificial achylia induced by total gastrectomy for the relief of gastric carcinoma, without evidence of recurrence of the malignant disease. Such a case has been reported from the Mayo Clinic by Hartman,[4] and 5 such instances are mentioned by Hurst and Bell in their article referred to below. Already certain animal experiments are under way by my colleagues, Dr. Haskell and Dr. Courtney, in the department of physiology of the Medical College of Virginia, to determine the blood changes that may follow total gastrectomy in dogs.

VI. The Relationship of Achylia Gastrica to Combined Sclerosis of the Spinal Cord. The relationship of achylia gastrica to pernicious anemia having been established, as well as the association of pernicious anemia with combined spinal sclerosis, it is strange that the relationship of achylia gastrica to combined spinal sclerosis has not been noted long ago; yet careful search of the literature failed to elicit any reference to this interesting association until most recently, when my attention was directed to the excellent and conclusive monograph of Arthur F. Hurst and J. R. Bell,[5] published in the neurological journal *Brain*, in October, 1922. These authors report 8 cases of combined spinal sclerosis, in all of which gastric analysis by the fractional method showed an absence of free hydrochloric acid. The test was repeated in 3 of the cases with the same result. They quote L. F. Barker[6] as having found complete achlorhydria in 2 cases of combined spinal sclerosis, and also mention a personal communication from Dr. J. F. Wilkinson, of Melbourne, who found achlorhydria in a patient

with digestive disturbances one year before the first sign of combined spinal sclerosis appeared.

For purposes of control, Hurst and Bell made gastric analyses in a series of 8 consecutive cases of disseminated sclerosis and 9 consecutive cases of tabes dorsalis. In these 17 cases achlorhydria was not found except in one tabetic. When the well-known frequency of achylia gastrica is considered no special importance can be attached to this 1 case out of 17 patients. These authors say, further: "In 3 recent cases which presented features very suggestive of subacute combined degeneration a normal curve of gastric acidity was discovered. Each eventually proved to be a case of syphilitic disease of the spinal cord. These cases are analogous to 2 others, the only cases in Guy's Hospital in which a diagnosis of Addison's anemia had been made in spite of the fact that free hydrochloric acid was present in the stomach. At the postmortem no evidence of hemolysis was present, one being found to have infective endocarditis and the other, who died of lobar pneumonia, having microscopical changes in the spleen which were typical of Hodgkin's disease."

For the past several years, as indicated by the accompanying case histories, I have been greatly interested in my observation that achylia gastrica was an almost invariable finding in patients with acroparesthesias and symptoms of combined spinal sclerosis. In fact, this relationship impressed me as being as constant as the finding of achlorhydria in patients suffering from pernicious anemia. During this period the diagnosis of combined spinal sclerosis was made in the case of 1 patient who showed free hydrochloric acid present in the gastric contents. This patient, however, was seen only once, and because of insufficient observation the opinion formed of his neurological lesion was not considered conclusive. A certain proportion of individuals with achylia gastrica have few if any gastrointestinal symptoms, and in 5 of the 7 cases reported in this article it was the paresthesias, and not any abdominal complaint, that caused us to make the gastric analyses.

As is well known, and illustrated by the case reports in this article, combined spinal sclerosis occurs in many individuals who present no evidence of pernicious anemia. Woltmann[2] states that

only one-third of the patients suffering from subacute combined sclerosis of the spinal cord seen at the Mayo Clinic were found to have pernicious anemia, and quotes von Voss (1897) as finding about the same proportion of pernicious anemia cases in a series of collected cases of combined spinal sclerosis. In my series of 29 patients with combined spinal sclerosis, all of whom showed an achlorhydria, there were 14 instances of unquestioned pernicious anemia. Several writers, among them Cadwalader,[7] have shown that continued observation of patients suffering from combined spinal sclerosis will demonstrate the subsequent development of the characteristic clinical and hematological picture of pernicious anemia in a large proportion of the cases.

VII. The Pathogenesis of Combined Sclerosis of the Spinal Cord. In the most authoritative description of subacute degeneration of the spinal cord by James Collier,[1] published as recently as 1921, it is stated: "Little is known of the causal factors of the disease, and in the majority of the recorded cases the patients have been strong and healthy until the onset of nervous symptoms. In a considerable number of cases, however, symptoms pointing to gastrointestinal infection, such as vomiting, diarrhea, anorexia or constipation, have been prominent before the onset of the nervous symptoms."

The failure of clinicians to recognize the almost invariable association of achylia gastrica with combined sclerosis of the spinal cord has, no doubt, been due, as Hurst and Bell point out, to the fact that this nervous disorder has been chiefly investigated by neurologists, who were only interested in a minor degree in the associated anemia or gastrointestinal disturbances; while, on the other hand, the spinal changes observed in pernicious anemia have been investigated chiefly by physicians, whose interest was in the anemia rather than the spinal disease. The significant feature of the monograph of Hurst and Bell is the fact that they discuss the two groups of cases, combined spinal sclerosis and pernicious anemia, from a common standpoint, and that they endeavor to show that both depend upon the same underlying pathological processes, namely, oral sepsis, absence of free hydrochloric acid from

the stomach contents throughout digestion and consequent intestinal infection and intoxication.

In spite of the expressed views of many writers who continue to reiterate the earlier confused state of our knowledge regarding the etiology of pernicious anemia, there is every reason to believe that achylia gastrica not only accompanies and precedes the development of this malady, but that it is an essential predisposing cause. The secretion of hydrochloric acid by the stomach is one of Nature's chemical defenses against infection, and it is most probable that in all cases of persistent achylia gastrica there ensues, sooner or later, a chronic intestinal toxemia. This toxemia must be tolerated by many individuals for long periods of time, as achlorhydria is a very common finding. (My 451 cases of achylia gastrica occurred in a series of 4281 consecutive private patients subjected to gastric analysis, thus showing an incidence of $10\frac{1}{2}$ per cent.)

In other individuals, however, toxins are evidently produced, either from bacterial decomposition of the food that enters the intestines unprepared by the usual gastric digestion or from bacteria from the mouth and throat that pass through the achylous stomach uninhibited by the acidity of the normal gastric juice. Of such toxins, one variety may have an especial affinity for the bone marrow or other hemopoietic organs and give rise to a hemolytic form of anemia, while another may exert its effect on the nervous tissues with a point of vulnerability in the posterior and lateral columns of the spinal cord. In one individual the hemolytic toxin may predominate, in another patient the neurotoxin is chiefly manifested, while in not a few cases there is evidence of a reaction to both toxins, as is seen in the advanced case of pernicious anemia with cord changes.

The chief significance of this report of certain cases of combined sclerosis of the spinal cord associated with achylia gastrica, confirming abundantly the published findings of Hurst and Bell, is that it would seem to shed considerable light on the etiology of pernicious anemia. In combined spinal sclerosis we also find achlorhydria as an essential predisposing cause, a most constant factor that is lacking in certain other degenerative lesions of the

spinal cord, such as disseminated sclerosis and tabes dorsalis. In fact, as Hurst and Bell emphasize, the presence of free hydrochloric acid in any fraction of a test-meal is probably a decisive point against the diagnosis of combined spinal sclerosis in a doubtful case. The frequent association of combined sclerosis of the spinal cord and pernicious anemia would indicate that the absence of the protective power of the normal gastric juice may permit the elaboration of both a neurotoxin as well as a hemolytic toxin. Hence, combined spinal sclerosis and pernicious anemia may coexist in the same patient, or either disease may arise separately, depending on the character and amount of the toxins produced.

Many writers, especially those from Guy's Hospital, where Addison reported the first recorded cases of pernicious anemia, have emphasized the presence of oral sepsis in this disease ever since Hunter first drew attention to the subject over twenty years ago. Alveolar infection was noted in all of the 8 cases of achlorhydria and combined spinal sclerosis reported by Hurst and Bell, and reference to my present cases shows that infection about the teeth was present in 6 of the 7 patients. In this connection it may be significant to note that Hurst and Bell recovered a streptococcus from the duodenum with the Einhorn tube in 7 consecutive cases of pernicious anemia and in 4 consecutive cases of combined spinal sclerosis, while this same organism was recovered in only 3 out of 26 control cases.

VIII. The Prognosis in Pernicious Anemia and in Combined Sclerosis of the Spinal Cord. A point that should be emphasized is that true achylia gastrica is a persistent and probably permanent condition. I have had under frequent observation a woman, now aged fifty-two years, in whom I first found an achlorhydria in January, 1909, and in whom fifteen consecutive gastric analyses in the intervening years have continued to show the absence of free hydrochloric acid. This patient has taken dilute hydrochloric acid in teaspoonful doses with meals regularly for the past fourteen years and has never shown any anemia or spinal-cord changes. In common with all other clinicians, however, pernicious anemia has continued to be a fatal disease in my observation with the possible exception of one most interesting patient who had an achylia gastrica

in 1914, again in 1917, associated with a characteristic picture of pernicious anemia, intensive hydrochloric acid therapy since 1917 and a normal blood picture in 1923, although the achylia gastrica persists.

The outlook in cases of combined spinal sclerosis unassociated with pernicious anemia has impressed me as being much more favorable, that is, in those cases in which the achylia gastrica is recognized and appropriate treatment instituted. As mentioned above, among the 7 patients that form the basis of this article, 1 is subjectively cured, 2 are apparently well and 1 is greatly improved. These subjective results are particularly interesting in that the degenerative lesions in the spinal cord are probably permanent and the physical signs persist or very gradually recede. Hurst and Bell state that sufficient time had not elapsed at the time of their publication to report the final results of treatment, but that in 2 of their cases there had been no increase in the nervous symptoms and that in 1 of these patients the tingling of the feet and hands had almost disappeared and the ataxic and spastic gait had greatly improved, although the physical signs were unaltered.

These results in the expected outcome in combined sclerosis of the spinal cord are in striking contrast to the former views on this subject. In fact, Collier, in his authoritative monograph, already referred to, writes in 1921 that "There is no evidence that recovery from this disease occurs in any of its stages."

Taking into consideration all the various factors already enumerated, I am firmly convinced that every individual suffering from achylia gastrica is a potential case of either pernicious anemia or combined sclerosis of the spinal cord. I am equally convinced that treatment, while certainly encouraging in those patients having paresthesias and symptoms of pyramidal tract degeneration without anemia, finds its greatest usefulness as a prophylactic measure. In other words, every individual with an achlorhydria should receive regular and adequate amounts of hydrochloric acid with every meal, and this remedy should not be omitted or discontinued unless it can be shown by a subsequent gastric analysis that the stomach has renewed its secretory activity.

IX. The Treatment of Combined Sclerosis of the Spinal Cord and the Associated Achylia Gastrica. The essential part of the treatment in every patient with achylia gastrica is the artificial replacement of the hydrochloric acid secretion in the stomach. This is readily accomplished by administering dilute hydrochloric acid with each meal. The matter of dosage is of much importance and the pharmacopœial recommendation of 10 to 15 minims is obsolete and entirely inadequate. For the past fifteen years it has been my custom to order 1 teaspoonful of the official dilute hydrochloric acid, well diluted, with each meal, and after the introduction of the duodenal tube in making routine gastric analyses by the fractional method, I satisfied myself, experimentally, that this dose was sufficient. In certain cases, however, in addition to 1 teaspoonful of the acid with meals, I have ordered a second teaspoonful to be taken a half hour after the meal. Hurst and Bell reproduce certain charts to illustrate that 1½ drams of dilute hydrochloric acid are required in order to compensate for the deficiency of gastric juice, and state that the acid should be added in the proportion of 1 dram to 4 ounces of water in order to make a beverage the acidity of which is about the same as that of gastric juice. The acid is best administered in buttermilk, but may be taken in sweetened lemonade or orangeade or in iced tea. It is a rather unpleasant dose in plain water. The acid-containing beverage is sipped during the course of the meal and part of it may be reserved for the twenty- or thirty-minute period following the meal. The administration of pepsin, pancreatin or other digestive ferments, while quite appropriate, has never appeared to be of any special value, and I rarely employ them in these cases. I have found that it is advisable to prohibit eating between meals except for indulgence in acid fruits, which may be taken freely. Buttermilk, either the natural article or milk which has been artificially soured with lactic acid bacilli, may also be taken at any time, and is not only well tolerated in cases of achlorhydria, but seems to be particularly helpful.

Chronic foci of infection should always be sought for and eradicated if possible. Chronic infection in the gall-bladder is a rather frequent associated lesion in patients with achlorhydria. Chronic

cholecystitis was diagnosed in 49 of my 451 achylia cases, an incidence of 10.8 per cent, and was suspected in certain additional cases. Infection about the teeth and in the tonsils and accessory nasal sinuses and chronic appendicitis and chronic infection in the urinary tract are frequently to be found, and the possible special significance of oral sepsis has been emphasized above.

In combined sclerosis of the spinal cord, aside from the control of the associated achlorhydria, the treatment is purely symptomatic. Massage and graduated exercises may be employed and sedatives may be used if necessary. Special treatment directed toward an accompanying anemia will not be discussed here except to emphasize again that every individual with a true achylia gastrica is a potential case of either pernicious anemia or combined sclerosis of the spinal cord, and that adequate treatment with hydrochloric acid in such instances is a prophylactic measure of the greatest value in combating the hemolytic toxins and neurotoxins that sooner or later become manifest in probably every case.

Summary. In a study of 451 consecutive cases of achlorhydria there were 29 individuals with definite evidence of combined sclerosis of the spinal cord. Of these 29 patients 14 had pernicious anemia, 1 had pellagra, in 7 the observations were incomplete, leaving 7 patients that form the basis of this report.

Combined sclerosis of the spinal cord has been regarded as a disease of obscure etiology and hopeless prognosis. The study of these 7 cases would seem to show, however, that achlorhydria not only precedes and accompanies the development of this nervous disorder, but that it is in all probability an essential predisposing cause. Achylia gastrica thus appears to be as constant a finding in combined spinal sclerosis as in pernicious anemia. In 1 instance neurotoxins and in the other hemolytic toxins are evidently produced in the intestinal tract of the individual whose stomach lacks the protective or inhibitory action of the normal hydrochloric acid secretion.

The outlook in patients suffering from combined sclerosis of the spinal cord not accompanied by pernicious anemia appears to be very favorably influenced by persistent treatment with full doses of hydrochloric acid, together with the removal of such foci of

chronic infection as may be found. Of the 7 patients covered in this report 1 is subjectively cured, 2 are apparently well and 1 is greatly improved. There is good reason to believe that every individual with true achylia gastrica is a potential case of either pernicious anemia or combined spinal sclerosis. More emphasis should be placed on the importance of adequate hydrochloric acid therapy as an essential prophylactic measure in every case of achylia gastrica.

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DISCUSSION

Dr. W. S. Thayer, Baltimore: I would like to express my deep interest in Dr. Vanderhoof's report. We know that pernicious anemia is preceded by diarrhea associated with anacidity of the gastric juice. This is present in almost all pernicious anemia cases. Cord changes are not infrequent in pernicious anemia and are often the first to be noted. In the instances in which cord changes have been found with achylia gastrica, in Dr. Vanderhoof's series, the fact that they have been held in abeyance or materially improved for years is a very interesting result.

Dr. B. W. Sippy, Chicago: I would like to know how much hydrochloric acid Dr. Vanderhoof gives. Our patients cannot take much by mouth because the pharynx will not tolerate it. It required 900 drops to digest a meal, and that is practically impossible to administer clinically. Would the small doses that he gives have much influence on the bacterial flora of the intestinal tract. It is very difficult to reason from cause to effect. We have heard of the fly who sat on the axle of the chariot wheel

and said, "What a dust I am causing." We must be careful that we are not attributing too much effect to very small doses.

Dr. H. S. Plummer, Rochester, Minn.: A large number of people are born with a diathesis whereby they have no hydrochloric acid. These people are naturally prone to develop certain clinical pictures—a scaly skin, anacidity and with a basal metabolism 15 to 20 per cent below normal. Perhaps the mother comes in and she shows very low basal metabolism. Arthritis and creaky joints are apt to be seen in these cases.

Dr. Vanderhoof (closing): For the past fifteen years we have been giving large doses of dilute hydrochloric acid in all cases of achylia gastrica. Ordinarily we prescribe a teaspoonful of the acid with each meal. When the duodenal tube first came into general use we tried giving patients with achlorhydria a dram of dilute hydrochloric acid with an Ewald test-breakfast and then extracted specimens of the gastric contents at intervals and satisfied ourselves that this dose of hydrochloric acid was sufficient. The observations in the patients with achlorhydria and combined spinal sclerosis came about naturally as the result of the routine administration of the hydrochloric acid. It did not occur to us in the beginning that the spinal-cord symptoms would be in any way benefited. We were therefore quite surprised, as well as impressed, by the striking improvement in 4 of the 7 patients reported in this paper.

AN EXPERIMENTAL STUDY OF MULTIPLE SCLEROSIS

By JOSEPH COLLINS, M.D.

AND

HIDEYO NOGUCHI, M.D.

NEW YORK

I. Clinical History and General Discussion

By Joseph Collins, M.D.

Hysteria and disseminated sclerosis are the nervous diseases of mystery. They are half-sisters, who reveal their relationship in the way they carry on. The greatest master of modern neurology courted them so assiduously that his name is indissolubly linked with both of them. He did not succeed in making them yield the secret of their being, and his successors have not succeeded. Now that syphilis is being forced into the category of curable diseases, and now that there is hope that we shall be able soon to shape and control by serum and antitoxin diseases caused by cocci and bacilli, hysteria and disseminated sclerosis are the two diseases of the nervous system upon which the physician and bacteriologist may concentrate their exploratory urge.

An instructive lesson may be learned from the history of disseminated sclerosis in this country. Less than a generation ago it was thought to be a rare disease. Less than a generation ago there was scant recognition of neurology, of its claim in college and hospital, and of nervous diseases in the clinic or in private practice. Today it is generally admitted that disseminated sclerosis is one of the commonest organic diseases of the nervous system, and today the teaching of neurology has a place commensurate with its

importance in the medical curriculum. In proportion as patients complaining of motor disorder have been examined carefully, methodically, and repeatedly, so have the statistics that establish the frequency of the disease come forth.

The first important contribution to our clinical knowledge of the disease was recognition of the fact that the *formes frustes* of Charcot, the aberrant or atypical forms of the disease, were the rule, not the exception; and that the so-called classical form of the disease, displaying itself in spastic extremity, scanning speech, intention tremor, and nystagmus was the exception, at least in the early stages of the disease.

The second important contribution was that the majority of cases diagnosticated myelitis—acute, subacute, and chronic—were in reality cases of disseminated sclerosis.

The third and very important contribution was the demonstration that many cases of paraplegia, monoplegia, and transitory disturbances of sensation labeled hysteria were cases of disseminated sclerosis.

And, finally, a significant clinical fact was recognized when we learned that disseminated sclerosis sometimes pursues a most extraordinary course: that is, not only does it cease to progress, but it practically ceases to be; and the patient, obviously helpless and apparently hopeless, sheds all manifestations of disease and returns to the engrossments and diversions of ordinary life. Unfortunately this is the exception, not the rule.

It would be an interesting chapter to give the details of how these steps were taken and who was most instrumental in accomplishing them, but I have no intention of doing it here.

All that we know of the occurrence of the disease can be summarized in a sentence: It is a disease of early maturity; it affects males somewhat more frequently than females; it occurs oftener in those who do skilled manual labor than it does in ordinary laborers and brain workers; and it is encountered oftener in northern countries—Great Britain and northern Europe and the northern part of the United States—than in southern. It has followed infectious disease and trauma in such a considerable portion of the cases that it has been thought that there is a causal relation-

ship between these two incidences and the occurrence of the disease, but it is doubtful. The probabilities are that there is some specific cause of disseminated sclerosis.

Disseminated sclerosis may cause symptoms that parallel those of any and every organic disease of the central nervous system. Every individual between the ages of fifteen and forty-five who complains of motor disturbance of any sort (tremor, spasticity or enfeeblement), or of sensory disturbances (tingling, numbness and other paresthesia), especially if they are transitory and associated with motor disorder, should be suspected of having disseminated sclerosis.

With just the same certainty that the loss of the pupillary light reflex indicates syphilis of the nervous system, so does the loss of the abdominal reflex suggest disseminated sclerosis; and as we seek corroboration of a diagnosis of syphilis of the nervous system in the individual whose pupils have ceased to respond to light by examining his tendon-jerks, investigating his sensory perception, and testing the reaction of his serum, so do we search in the individual whose abdomen no longer responds to gentle stroking by investigating his superficial and deep reflexes, his ocular mobility, the steadiness of purposeful manual movements, and the rhythm of his articulation. If his superficial reflexes are diminished, his tendon reflexes increased, his eyeballs oscillatory on attempted lateral fixation, if the rhythm of his speech is disturbed, or if he has intention tremor, the diagnosis of disseminated sclerosis may be made with much certainty.

The most constant early symptom of disseminated sclerosis is fleeting, subjective sensory disturbance. It is rarely elicited save on closest inquiry. The most constant symptom which the patient relates is easily induced fatigue, weakness and stiffness of one or more extremities. It is always associated with increased tendon-jerks and often with the Babinski big-toe phenomenon and allied signs.

The cranial nerves that are most frequently disordered are the first, the third, and the sixth, and the display is in lacunar losses of acuteness of vision, central and circumcentral scotoma, transitory diplopia and nystagmus. The most pathognomonic sign of

disseminated sclerosis is pallor of the temple discs. So far as we know, it is found in no other disease.

The islets of disseminated sclerosis may occur in any part of the central nervous system; hence evidences of encroachment upon and destruction of any part of the central nervous system may be a symptom of disseminated sclerosis.

No one is ever justified in giving arbitrarily an unfavorable prognosis in disseminated sclerosis, it matters not how helpless the victim of the disease may be, and inasmuch as many have taken in hand to set forth a declaration of other import, I relate the following experience:

Twelve years ago there was brought to the Neurological Institute a young athlete, bedridden of spastic paraplegia for nearly a year. Because of fairly definite sensory disturbance it was thought that he might have a tumor pressing upon the spinal cord. Repeated examination and protracted observation showed that he had, in addition to the spastic paraplegia and its customary concomitants, loss of abdominal reflexes, nystagmus, enfeeblement of the left upper extremity, and circumcentral scotoma. The vesical sphincter was irritable, the rectal sphincter sluggish. The symptoms had existed for nearly a year, and the state of helplessness which caused so much anxiety to him and to his family was of four months' duration. Repeated inquiry finally elicited the fact that when he was in high school, eight years before, he had had an attack of "lameness" that laid him up for several weeks, and that at that time his feet and hands were numb.

This man has now been at work for ten years, the advertising manager of a large and engrossing business. He admits that he plays a good game of golf, but the writer sometimes beats him.

Eighteen months ago, Dr. Noguchi suggested that I select a number of cases of disseminated sclerosis and send him blood and cerebrospinal fluid, in order that he might test the alleged spirochetal origin of the disease. I selected 8 cases.

Case I.—A man of twenty-three, who had had a dishonorable discharge from the army. The discharge regrettably reflects upon the clinical acumen of some of our profession. He was looked upon as a malingerer. If spasticity, paralysis, exaggerated tendon-jerks, the Babinski sign, loss of abdominal reflex, nystagmus, scanning speech, and intention tremor

constitute competent testimony, he has disseminated sclerosis. He was a recent case, therefore, and there is nothing further interesting about him.

Case II.—A "classical" case of disseminated sclerosis, a celibate of thirty-five. The noteworthy feature was that he had had profound osteomyelitis as a boy, and recovered after a prolonged tarry in the Rocky Mountains.

Case III.—A man, aged twenty-seven years, whose symptoms had existed two years. He was an "atypical" case; that is, he had no nystagmus, intention tremor, nor scanning speech, but he was a genuine example of disseminated sclerosis nevertheless.

Case IV.—A youth, aged twenty-two years. He had more of the so-called typical objective symptoms than Case III, and few would doubt the validity of the diagnosis.

Case V.—A woman, aged forty years. Her symptoms had lasted only two years, and one should always be on the lookout not to mistake such symptoms in an individual of forty for disease of the blood or bloodvessels. But, as in so many of these cases, it was found on close inquiry that it was *this attack* that had existed two years. She had had transitory symptoms when she was twenty-six, and again when she was thirty-one.

Case VI.—A painter, aged thirty-six years. His was a doubtful case. It was thought that his symptoms might be due to lead-poisoning, but we never were able to recover lead from the urine and there was no stippling of the blood corpuscles. As time goes on one is permitted to say with more assurance that his is a case of disseminated sclerosis.

Case VII.—A man, aged thirty-four years, whose symptoms had been in existence three years, and who had never had any indication of a remission.

Case VIII.—A man, aged forty-six years, ill during seven years. His disease had frequently been diagnosed as lateral sclerosis, and nobody knows just what that means. Most cases diagnosed as lateral sclerosis are cases of disseminated sclerosis.

Six of our cases were Jews and two Gentiles. This will make reflect only those who have never been to the Neurological Institute or who are not familiar with its statistics.

II. Experimental Results in Animals Inoculated with Blood and Cerebrospinal Fluid

By Hideyo Noguchi, M.D.

The possibility is gaining ground that disseminated sclerosis is of infectious origin. Bullock,[1] as early as 1913, claimed to have reproduced the disease in laboratory animals, but it was not until Kuhn and Steiner[2] announced, in 1917, their finding of a spirochete in the blood and organs of guinea-pigs and rabbits inoculated with spinal fluid or blood or both from 4 exacerbation cases (3 fresh and 1 recent) that the problem appeared to be narrowed down to a definite microörganism. The spirochete was observed in fresh preparations under the dark-field microscope, also in smears stained by Loeffler's technic for staining flagella, and occasionally in alcohol-fixed organs stained by the Levaditi method. The organism was designated by Kuhn and Steiner as *Spirochæta argentinesis*, from the Latin name of Strasburg, where the work was carried on.

The description of *Spirochæta argentinesis* is of interest because of the rather inconstant morphological features of the organism. By dark-field illumination it was said to vary in length from a fraction of the diameter of the red cell of the infected animal to a whole diameter, while in width it was more delicate than *Leptospira icterohæmorrhagiæ* of Weil's disease, being often of extraordinary thinness. There were often highly refractile balls at both ends. Some specimens showed a loop at the end or along the course of the body. The movements were somewhat wormlike, moderately active, but seldom rotatory, as in the case of *Leptospira icterohæmorrhagiæ*. In stained preparations a small, delicate, straight projection of varying size was observed, resembling a flagellum. In Levaditi sections of the liver of animals the organisms appeared only in the bloodvessels, never in the tissue itself. Only a few isolated bloodvessels were involved. No spirochetes were found in human materials.

In guinea-pigs the disease lasted three days to twelve weeks from the time of inoculation to death. Paralysis was usually present. In rabbits the symptoms consisted of emaciation, inactivity,

ruffled fur, paroxysmal drowsiness, increased reflexes, and paralysis before death. No remarkable changes of organs were observed at autopsy, and no organisms grew on culture media.

Siemerling,[3] in 1918, claimed to have observed under the dark-field microscope a similar spirochete in the brain of a man who died of multiple sclerosis. Büscher[4] and Speer,[5] in 1921, reported each one positive finding. Speer's case was diagnosed by histological examination of the brain and cord and the spirochete was found under the dark field in a fresh preparation from a grayish-red focus in the medulla oblongata. A number of larger forms were seen, which in appearance recalled the tetanus bacillus or spermatozoa, or had lateral buds. Some regular forms resembling *Treponema pallidum*, but perhaps shorter and thinner, were also described. The spirochetes remained active in the smear for seven hours. Speer, like Siemerling and Büscher, found no spirochetes in sections (Levaditi).

Simons,[6] in 1918, reported positive transmission to rabbits with blood. Marinesco,[7] in 1919, saw active spirochetes in the fluid from the fourth ventricle of guinea-pigs dying of paralysis within three to four days after intracerebral inoculations of blood serums from 2 cases of multiple sclerosis. Marinesco failed, however, to obtain similar positive results on repeating the experiments.

Kuhn and Steiner[8] studied 13 additional cases and found the spirochete in 4 of 6 early cases and in 1 exacerbation case, but none in 6 old cases. By inoculating blood intraocularly, positive transmission to rabbits and guinea-pigs was obtained in 6 cases. The authors report successful demonstration of the spirochetes in tissues by silver impregnation.

Birley and Dudgeon,[9] in 1921, obtained uniformly negative results with materials from 35 carefully selected cases of multiple sclerosis. Stevenson[10] examined 37 sections from 4 cases, stained by Jahnel's silver-impregnation method, but found no spirochetes.

Kalberlah[11] studied 2 relatively recent cases; 1 of the rabbits inoculated with cerebrospinal fluid from the first case showed symptoms of paralysis and a spirochete was found in the circulating blood, while in the second case numerous spirochetes of indisputable morphology were demonstrated in the bloodvessels and liver tissue.

Pettit[12] succeeded in producing a fatal disease in rabbits, and in 1 instance in guinea-pigs and a monkey, with cerebrospinal fluid from 4 cases, and organisms resembling spirochetes were found in the cerebrospinal fluid of the animals. In one instance he was successful in transmitting the disease from rabbit to guinea-pig, guinea-pig to rabbit, and monkey to rabbit.

Gerson[13] does not regard the finding of spirochetes in certain instances as satisfactory evidence that they have a specific etiological relation to multiple sclerosis, and calls attention to the fact that certain cases of syphilis simulate typical multiple sclerosis, whence confusion in diagnosis may have occurred in the instances in which spirochetes were found.

Our purpose in taking up the question of the etiology of multiple sclerosis was, if possible, to confirm and extend the observations of Kuhn and Steiner and to study the spirochete by means of cultivation. As indicated in the experimental protocols presented below, the results were disappointing, being chiefly negative.

The histories of the 8 cases available for study have been outlined by Dr. Collins. The general plan of the experiments was as follows:

The blood and cerebrospinal fluid in every instance were utilized within a few hours from the time of withdrawal. The blood was citrated, oxalated, defibrinated, or used in the form of clear serum from the clot. The materials were sometimes inoculated separately into rabbits and guinea-pigs, but more frequently a mixture of blood and spinal fluid was employed. In most cases a combination of two or more modes of inoculation was used. A rabbit or guinea-pig was usually injected both intracerebrally and intraperitoneally, and the rabbits, in addition, often received some material intravenously and intratesticularly. Intraocular instead of intracerebral inoculations were performed in some instances. Cultures were set up with ascitic fluid tissue medium such as that employed for the cultivation of *Treponema pallidum* and other anaërobic treponemata,[14] also in the medium used for growing relapsing fever spirochetes[15] and in leptospira medium.[16]

Material from Case I was inoculated on two occasions, 6 guinea-pigs and 3 rabbits being used in the first instance and 4 guinea-pigs

and 4 rabbits in the second. Nothing of note developed. In Cases II, III, IV, V and VI inoculations were made in each instance into 4 guinea-pigs and 4 rabbits, with similar negative results. In Case VII, 2 guinea-pigs and 4 rabbits and in Case VIII, 3 rabbits were inoculated, also without any result which can be interpreted as experimental reproduction of multiple sclerosis.

Among the guinea-pigs a number of animals showed one or more periods of high temperature, lasting sometimes for several days and being followed by irregular fever. Cultural examination of these animals usually revealed infection with a strain of paratyphoid or hog-cholera bacillus. Some recovered, others remained alive, but showed marked emaciation. Rabbits also suffered to some extent from secondary infection. Some died of rabbit septicemia, the cultural and pathological findings being typical of that infection. Occasionally a peculiar loss of equilibrium was observed, but this symptom is not uncommon in infection with *Bacillus lepisepticus*.

Repeated dark-field examinations of the blood and cerebrospinal fluid, while perfectly fresh, failed to reveal any spirochetes. Most of the culture tubes remained free from ordinary contaminations, but no spirochetes were found in any of them. Injections of the contents of the culture tubes into guinea-pigs and rabbits produced no symptoms of significance. Dark-field examination of peripheral or heart blood of the inoculated guinea-pigs and rabbits showed no spirochetes. In addition to blood, emulsions of liver, spleen, kidney, adrenal glands, lymph nodes, and brain from guinea-pigs or rabbits killed at the height of fever were carefully examined under the dark-field microscope without a single positive finding. The usual morphological elements were present in the citrated and defibrinated blood, in suspensions of the clot and in organ emulsions, elements such as frequently deceive even the skilled microscopist when seen by dark-field illumination. Errors from this source have occurred in the past and are particularly apt to occur when the illumination is partial, the delicate, tremulous, beaded filaments of varying length and width appearing as if moderately motile and behaving not unlike the leptospira group of spirochetes. By full central illumination they are shown to be

thinner than the leptospiras. These filaments are abundant in blood suspensions kept for a time at room temperature and there are many swimming forms not attached to erythrocytes. They are undoubtedly derived from altered red corpuscles. They cannot be stained by Giemsa's solution but are sometimes brought out by Loeffler's stain for flagella. It is, of course, unlikely that Kuhn and Steiner interpreted these filaments as delicate spirochetes of the leptospira group, yet the description of their spirochete strikingly suggests the forms just referred to.

The negative results obtained in the present investigation indicate that the demonstration of *Spirochæta argentinesis* and the experimental reproduction of multiple sclerosis in guinea-pigs and rabbits are difficult. Renewed effort with material from fresher cases is desirable.

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DISCUSSION

Dr. Amoss, Baltimore: We have obtained results which we cannot explain. Spinal fluid from a patient with acute disseminated sclerosis was injected intracerebrally into 5 rabbits. On the sixth day 3 of the animals appeared normal but rather restless, and died suddenly within one hour. No organisms were found. The temperature of the 3 animals reached 106°, then dropped to subnormal before death. Autopsy showed extreme congestion of the brain with slight hemorrhages. Dark-field examination revealed no spirochetes. We carried this forward through 5 animal passages, resulting in the death of the animal in six to nine days, but our findings remain indefinite.

Dr. Noguchi (closing): I have used 16 animals altogether. I think the experiment of Dr. Amoss is interesting and suggestive. Animals do not die like that unless something definite has happened. That appears to be promising.

A STUDY OF REFLEXES ARISING IN THE INTEGUMENT AND CAUSING SENSORY AND MOTOR DISTURBANCES IN NORMAL ANIMALS

A CONTRIBUTION TO BROWN-SÉQUARD'S EPILEPSY[1]

(ABSTRACT)

By JOHN AUER, M.D.
ST. LOUIS

BROWN-SÉQUARD was the first to report that operative insults to the nervous system such as lateral hemisection of the cord, section of the dorsal columns and section of one or both sciatic nerves produced, after a certain lapse of time, a variety of interesting motor disturbances in the guinea-pig. These disturbances were characterized by attacks of complex, coördinated, tonic and clonic contractions of the muscles of the head, neck, trunk and legs. The motor discharges occurred spontaneously or as the result of pressure stimulation of a certain receptive field of the skin which Brown-Séquard called the "epileptogenic zone." This area comprehended roughly the side of the face below the eye and extended backward, including the scapular region. The zone was unilateral after unilateral lesions and was always located on the operated side when the cord was involved; after damage to the brain, however, the "epileptogenic zone" shifted to the opposite side. In addition to the manifestations mentioned, Brown-Séquard also described a transient "blepharospasm," a "bronchorrhea" and the expulsion of feces, urine and semen during the attack. Brown-Séquard never observed the symptoms in normal guinea-pigs, but Graham Brown in his excellent analysis of these motor phenomena mentions briefly some suggestive reactions observable in the normal guinea-pig;[2] these appear to have been slight and inconstant, however.

The chief symptoms of the complex known as "Brown-Séquard's epilepsy" may be obtained in the normal, non-operated guinea-pig provided certain conditions are fulfilled: (1) The animal must

[1] From the Department of Pharmacology, St. Louis University School of Medicine.
[2] Brown, T. Graham: Quart. Jour. Exp. Physiol., 1910, iii, 144.

be accustomed to his surroundings, including the experimenter; (2) visitors, abrupt movements, unaccustomed noises and apparently also odors and sudden vibrations must be avoided, otherwise the typical reactions following tactile or pressure stimuli of the skin may be largely or entirely inhibited. The length of time necessary to fulfil these conditions varies considerably in different animals, especially when only touch stimuli are employed.

Touch stimuli were applied chiefly by means of long bristles mounted on handles; pressure stimuli were produced by pushing a long, slender, wooden rod, one-eighth to three-sixteenths of an inch in diameter, against the skin; the stimuli were both of short and long duration and were applied frequently.

The sites where symptoms are most easily elicitable are: (1) A small area just posterior to the angle of the jaw and below the ear, and (2) an area just anterior to the pelvis and above the femur when the animal is in a squatting position. Pressure stimuli are most effective especially in the beginning. Either side of the body may be stimulated effectively.

Some of the reactions obtained after pressure stimuli in the lumbopelvic area are as follows: A lateral arching of the body, the nose of the animal approaching the site stimulated, with rotation of the head so that the plane of the lower jaw is turned toward the body. Associated with this arching of the body the hind leg of the side stimulated is usually flexed suddenly and strongly at hip and knee, the foot is dorsally flexed at the ankle while the toes may be extended and spread far apart, or the toes may be close together and slightly flexed. At the same time the hind leg of the opposite side is usually strongly and forcibly extended, raising the posterior half of the body, or the leg may be strongly abducted. The hind leg of the side stimulated may execute a series of scratching movements, the toes moving toward the jaw of the same side; at times the toes actually scratch the jaw and then the toes are usually spread apart. At other times the toes merely approach the jaw and then in general are not spread; when this occurs the dorsal lift of the femur is apparently especially marked and the movement now resembles the thigh wiping-reflex of the frog. The scratch reaction may consist of one to eight, and perhaps more, exceedingly

rapid flexions and extensions of the thigh, leg and foot. In animals which have been tested for months this pressure stimulus causes the lateral curvature of the body and neck, but often both hind legs are violently extended at the same time, so that the animal is hurled into the air; the animal, however, always righted itself in mid-air and was never observed to fall on its side or to roll over.

Pressure stimuli just posterior to the angle of the jaw usually cause a general shaking of the body similar to that executed by a wet dog, with more or less general erection of the hair; wiping of the head and face with the front leg of the side stimulated, the head being rotated toward the non-stimulated side, or a more or less marked scratch reaction of the hind leg of the same side may occur. Often the front leg of the side stimulated may execute a series of rapid back-and-forth shaking movements.

Touch stimuli may give the same motor reactions, but in addition they permit the observation of other responses which are partially masked when pressure stimuli are applied; some of these are chewing motions; slow, audible, grinding movements of the teeth; dorsal or ventral nodding movements of the head; sneezing associated with unilateral or bilateral wiping of the nose; a general coarse tremor; short convulsive contractions of the muscles of the trunk, neck and legs which raise the trunk slightly from the floor, the head being flexed ventrally. Associated with the latter movements one may observe at times a spasmodic, powerful retraction of the angles of the mouth accompanied by a wide separation of the jaws and strong closure of the eyelids.

Increased defecation and urination may be readily observed in these animals after repeated pressure or touch stimulation. In 2 instances several drops of a milky fluid suddenly issued from the nares (a naris?) and fell upon the reflecting mirror of the observation cage where the animal was being tested. The ejaculation of semen was never seen by me.

From this brief description it will be perceived that the so-called "incomplete attack" of Brown-Séquard may readily be obtained under proper conditions in normal guinea-pigs. The absence of the "complete attack" is probably attributable to the normal muscular balance of these animals.

Though the curious reflexes which tactile and pressure stimuli of the integument elicit in the normal guinea-pig were clear and unmistakable in their expression, yet their tentative explanation proved most unsatisfactory until an observation in this study gave a clew. It was then realized that many of the described responses were not the immediate answers to the original stimulus but were the result of a referred, apparently centrally radiated, sensory impression which the primary tactile or pressure stimulus had called forth. A few experimental results will illustrate this statement:

When the skin covering the right costal margin is gently rubbed with the rounded end of a slender wooden rod, the animal being free in a spacious box, then under proper conditions the animal sooner or later swiftly wipes the right front foot backward once or twice, the toes being spread apart. Repetition of the stimulus then causes a very rapid shaking of the foot back and forth; on still further stimulation the right front foot is lifted and the animal seizes the nail of the inner toe with its teeth and pulls vigorously; at times it may seize all four front toe-nails in rotation and strip them with its teeth. Stimulation on the left costal margin causes the same reaction with the left foot. Not infrequently a crossed response to the stimulus is observed: Stimulation of the right costal margin calls forth the reaction in the left front foot or in the right front foot when the left costal region is stimulated.

Pressure stimuli applied to one lumbopelvic area may cause some or all of the following responses: Lateral arching of the body, the head approaching the site of stimulation; repeated rapid seizure of the hair at the point stimulated by the lips and teeth as if seeking a parasite; the mirror picture of the above, the animal seizing the hair at the symmetrical point on the opposite, non-stimulated side; the lateral aspect of the jaw on the side stimulated is vigorously scratched by the hind leg; the ear, top of the head and the lateral aspect of the jaw are wiped repeatedly by the front foot of the stimulated side, the head being rotated so that the nose is turned toward the non-stimulated side; the wiping movement is repeated by the front foot of the opposite side or the animal may sit up on

its haunches, wiping the top of the head, the ears and jaws, simultaneously or alternately, with its front feet.

Another example of dyschiria is seen when the sacropelvic portion of the back is stimulated by repeated tactile stimuli (bristle); the perineal region is suddenly depressed and moved forward, or occasionally both hind legs are extended anteriorly and by means of its front legs the animal propels itself forward, scraping the perineal area on the floor.

An instructive series of motor responses, apparently due to a related, central shifting of sensory stimuli, may be seen when the animal is examined in a small box whose floor and sides are formed by half-inch wire netting; the box at each corner rests on columns seven inches high, and these bases also support an inclined mirror which permits easy observation of the animal's ventral aspect. Repeated stroking of the sole of the right hind foot with the tip of a wooden rod may cause all or some of the following reactions: The right hind leg is first lifted abruptly and set down with a stamp; on continuation of the stimulation the same leg is suddenly extended forward and one nail of the toes, or all of them in rotation, are seized by the teeth and vigorously pulled; the stimulation being continued, there may be only a slight or no movement of the stimulated right hind foot, but the right front foot is lifted and one or more toe-nails seized and pulled; still later a crossed response is obtained and now the left hind leg is extended forward and the toe-nails seized and pulled by the teeth; still later, the stimulation of the right sole being continued, the animal scratches the right shoulder with the hind leg.

The sensations caused by tactile or pressure stimuli of the integument are not only referred to other skin areas, but they may be referred to mucous membranes. For example, after tactile stimulation of one flank the animal may suddenly rub the same or the opposite or both sides of the nose with circular movements of the radial aspect of the fist or fists. There are also sneezes, and in 2 instances drops of milky fluid suddenly issued from a naris (nares?). Furthermore, slow, chewing motions of the jaws are very common after tactile stimulation of the skin; occasionally one hears a slow

grinding of the teeth. At times the animal seizes and chews anything available in the neighborhood: sawdust, hay, the wooden sides of the container or the netting itself. The wide opening of the jaws occasionally observed may possibly also be associated with a type of sensation referred to the buccal cavity.

In addition to these manifestations there is evidence that at least one of the special senses apparently may be involved. When an animal is tested with tactile or pressure or both types of stimuli, one may see that the animal suddenly pauses, raises its nose high in the air and samples it in various directions; or the animal abruptly sniffs interestedly in the sawdust, often spreading the sawdust by lateral sweeps of the front legs, to facilitate its olfactory investigation.

It is believed that these observations may be of value in aiding the interpretation of other normal and abnormal reflex activities. It is also possible that some of the paresthesias observable in the human subject may be due to the central progression of stimuli whose origin is an irritated skin area more or less distant from the site to which the sensation is referred.

The material upon which this study is based consists of about 60 guinea-pigs, chiefly males. All of them were under close daily observation for months.

ERYTHREMIA (POLYCYTHEMIA RUBRA VERA).

The Development of Anemia; the Relation to Leukemia; Consideration of the Basal Metabolism, Blood Formation and Destruction and Fragility of the Red Cells.*

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Polycythemia rubra vera (Vaquez-Osler disease), appropriately termed erythremia by Osler[1] and others, is recognized as a disease due to excessive erythroblastic activity of the bone-marrow. This disorder, primarily of the red cell elements of the marrow, is comparable to that of the white cell elements of the marrow known as chronic myelogenous leukemia. Both conditions may be looked upon as neoplasms of the hemopoietic tissue.

Blood Formation. The excessive activity of the bone-marrow in erythremia is evidenced by the fact that cases upon which a careful autopsy has been performed have shown great increase in the amount of red marrow which is actively hyperplastic and which may be altered in character from normal. Evidence of the increased activity of the marrow is shown in the living subject by the presence of both abnormal and immature red cells in the

* This paper is No. 30 of a series of papers on the Physiology and Pathology of Blood, from the Harvard Medical School and allied hospitals; a part of the expense of which has been defrayed by a grant from the Proctor Fund for the study of chronic disease.

circulation. In the literature, one not infrequently finds the statement that the blood is essentially normal and that immature red cells are seldom seen. It has been our experience, however, in accord with that of many others, always to find the red cells changed from normal, and in most instances to observe evidence of immaturity. This statement is based upon observations made upon 15 cases, and the blood of some has been studied many times over a period of seven years. The change from normal may, however, be slight, and consist of only a little unusual variation in size, with an occasional polychromatophilic red cell. Greater changes are often seen, a feature being an unevenness in the depth to which the cells take the stain, dependent, we believe, upon cells of different ages. Achromia may be marked, and great variations in the relation of the hemoglobin to the red count occur with the color index less than 1. At times there appear many cells showing polychromatophilia; some very deeply and others very slightly basophilic. Macrocytes and microcytes may occur in varying numbers and proportions. Blasts not infrequently occur. Yet in some instances reticulated red cells (young cells) may be actually decreased, as occurs in experimental polycythemia, as noted by Robertson,[2] and Krumbhaar and Chanutin,[23] and as we have observed at the height of remissions in pernicious anemia. It is to be realized that the numbers of young red cells entering the peripheral blood depend upon the state of the marrow at the moment, and that their presence or absence does not indicate the fundamental character of the marrow.

Further evidence of increased activity of the marrow in erythremia is shown by the leukogenic elements sharing in the process, as is witnessed postmortem by increase of the leukoblastic tissue. This leukoblastic activity is reflected in the peripheral blood by the almost constant finding of an increased white count and an increased percentage of bone-marrow leukocytes. It is not uncommon to find a few, and occasionally many, immature white cells in the circulation. The detailed appearance of the polymorphonuclear cells as well as the immature cells may deviate from normal, as shown by variations in their size and by the character of their

cytoplasmic granulations and nucleus. These features are of a type one may associate with hasty or abnormal formation.

The platelet elements of the marrow may also become involved in the disease process, in a similar fashion as they do in myelogenous leukemia. They may be increased in the blood stream, and even megacaryocyte nuclei may enter the circulation.

Plate I illustrates the character of the peripheral blood in erythremia, especially the erythrocytes.

In myelogenous leukemia, looked upon by many as a form of neoplasm, the abnormal proliferation in the marrow is readily reflected in the peripheral blood. It is argued by some (Ward[3]) that, because the peripheral blood in erythremia shows only occasionally such immature cells as blasts and that because extra medullary blood formation is often lacking, the proliferative process in this disease does not appear disorderly enough to support the theory that it is in the nature of a neoplasm

It is recognized that it is easier to influence the output of white-cell elements from the marrow than it is the red-cell elements. It is not necessary to assume that blasts and many immature red cells must appear in the circulation in order to conceive that erythremia is in the nature of a neoplasm The immature elements will appear according to the rate of growth-pressure of the marrow, as shown by Drinker.[4 5] From our studies, it is evident that, especially in cases of long duration and with the development of actual anemia, a very disorderly type of blood formation with extramedullary hematopoiesis may occur and be reflected in the peripheral blood. This would favor the conception that the disease is in the nature of a malignant hyperplasia.

It is reasonable to assume that signs of a very disorderly marrow are usually not observed, because it requires a long period of time before the condition becomes sufficiently pathological to permit a marked abnormality in the types of cells delivered from the marrow. Often before the condition reaches such a stage, patients may die from various results of the polycythemia *per se*. This situation is, perhaps, comparable to what occurs in pernicious anemia, in which there is a gross departure from normal blood

formation. If the peripheral blood or the marrow be examined in the height of remission or early in pernicious anemia, but little abnormality is observed, this transitory finding being in contrast to the so-called megaloblastic reaction, which is often extreme and observed in relapses.[6]

Cases Developing Anemia. Among the 15 cases of erythremia are 3 that have developed definite anemia and have served to clarify further our conception of this disease. These 3 cases were exceedingly similar; 2 are now dead 1 having come to autopsy. These cases, all women, had polycythemia (the red count being above 7,000 000 per cm. and frequently as high as 11,000,000 per cm.) with some splenic enlargement for a period of five years in 1, and for eighteen to twenty years in the other 2 cases. During this time they suffered from all of the usual and some of the unusual symptoms of the disease. In the course of about a year following the many years of polycythemia, the red counts of all 3 patients dropped, and the hemoglobin decreased to a relatively greater degree. The red cells fell to about 5,000,000 per cm., and the hemoglobin (calculated from the oxygen capacity) to about 85 per cent. Either coincident with or shortly following this drop, the spleens increased considerably in size, so that they then filled at least the whole left side of the abdomen. In 1 case this change occurred two years before death; in another, about six years before the postmortem examination. In the third who is now living in a reasonable state of health, the change took place about two years ago. In all cases, the red counts and particularly the hemoglobin continued to fall, although over a period of weeks a definite increase of the count to 8,000,000 per cm., followed by a further rapid decline to 3,000,000 per cm., occurred in the case that had the disease the shortest time.

Shortly before the death of 2 of the patients the red count was about 2,500,000 per cm. In the third case (now living), the count is 3,500,000 per cm. In all cases coincident with the development of the anemia, striking pathological changes were observed in the peripheral blood. During the period of anemia the red cells showed marked variation in size and considerable variation in shape. Microcytes were evident, though never in profusion.

Macrocytes of abnormal shapes occurred, and true megalocytes. In one blood these were very plentiful, so that the red-cell picture resembled that of a typical case of pernicious anemia, while the red-cell picture in all 3 cases suggested this disease. The unevenness in the depth of staining of the cells was usually striking. The numbers of polychromatophilic cells varied, as did the reticulocytes. Considerable increases were frequently observed. Various types of nuclear remains were present. Blasts were a feature; as many as 3000 per cm. were seen. All types were present, including some showing divided nuclei. With progression of the disease, more of these immature elements appeared in the blood stream.

The white-cell picture was one that may be seen in myelogenous leukemia. As the disease advanced, the white count tended to become higher and averaged 35,000 per cmm. From time to time fluctuations occurred, occasionally being quite extreme. All forms of immature myelogenous white cells appeared, some of which conformed to no standard type. The lymphocytes were distinctly few. It was not uncommon to see 10 per cent of myelocytes, sometimes more, while even myeloblasts reaching as high as 15 per cent were observed. During the anemic phase, the platelets fluctuated from distinctly above to even below normal. Free bits of megacaryocyte cytoplasm occurred, as well as occasionally a megacaryocyte nucleus.

The patients presented numerous features that are not commented upon here, as they are not distinctly related to the fundamental nature of their disease, except for the fact that all showed some enlargement of the liver.

Extramedullary blood formation has been reported in erythremia, with partial myeloid transformation of the spleen in some cases, but perhaps not to the degree found in our case. Dr. Wolbach has made a detailed examination of the tissue in the case that came to autopsy. This patient had suffered from her disease some twenty odd years. The spleen weighed 3200 gm. It presented a remarkable picture of myeloid transformation, which intimately resembled that of myelogenous leukemia. The liver also had the appearance of a leukemic liver of a myelogenous type. Signs of red cell formation in clumps of myelocytes were found to a less

extent in the lungs, some of lymph nodes and adrenals. The marrow was actively erythroblastic, and was filled with an excess of myelocytes and immature elements. Megacaryocytes were abundant. The 2 cases that have not come to autopsy would appear to be entirely similar to this one that did.

Relation of Erythremia to Leukemia. The resemblance of erythremia to leukemia has already been alluded to. From the clinical observations, the case that came to autopsy seems unquestionably one of erythremia, and the pathological findings that intimately resemble those of leukemia heavily support the hypothesis that the condition is analogous to this latter disease and that they bear a close relationship. Previously, we[7] have referred to this relationship, as have others.[8 9 10] Blumenthal's[11] well-known case of polycythemia, with many myelocytes in the peripheral blood and the finding at autopsy of excessive leukoblastic activity, has often been referred to in such discussions.

As mentioned before, some relatively slight degree of myelocytosis is often present with polycythemia, and the leukoblastic elements of the marrow are increased and involved in the disease process. A few other cases are recorded that resemble Blumenthal's and our 3 cases referred to, with marked alteration in the formation of white cells. Rosin's[12] case, Herxheimer's[13] and Brieger and Forschbach's[13a] are examples that terminated with all the typical features of myelogenous leukemia. One of us has observed also a man who had a red cell count between 6,500,000 and 7,500,000 per cm. and a white cell count of about 20,000 per cm., with 15 per cent myelocytes, die a year later with marked anemia and the peripheral blood of leukemia. The typical findings of this disease were present at autopsy.

That a patient with typical leukemia may develop a distinct polycythemia is recorded in the literature, as shown by Winter[14] and also Ghiron's[15] case. It may be emphasized here that the megacaryocyte elements of the marrow share in the disease process of leukemia and erythremia, and that rarely in the former condition they may be relatively more involved than the white cells.[16] In such a condition, the blood may be flooded with megacaryocytes and their derivatives, the platelets, so that for the

time the disease process appears to be particularly confined to the megacaryocytes, as erythremia is to the red cells and leukemia to the white cells. The term piastrinemia has been given by Pianese[17] and Di Guglielmo[18] to such a condition. It thus appears that there occur cases of erythremia or leukemia that illustrate multiple varieties of varying degrees of primary pathological activity of myeloid tissue which usually conforms to a definite type.

Basal Metabolism in Erythremia. Before discussing blood destruction and the cause of anemia in erythremia, observations upon the basal metabolism will be referred to, because the increased metabolism that has been found is believed to be related to the pathological blood formation. There are but few records in the literature of the basal metabolism in erythremia; and so far but few determinations have been made in our cases. Abbott[19] found in 1 case the basal metabolic rate to be +16 per cent on one occasion, and +27.8 per cent five months later. Marsh[20] found +21 per cent in a case. Isaacs[21] has noted a basal metabolism of +35.2 per cent, on the average of several determinations, in a case with the red cell count remaining at about 9,000,000 per cm. The basal metabolism in our case with anemia that came to autopsy varied between +10 and +20 per cent two to four years before death. Six months before death it was +40 per cent. Two determinations on the other patient, who died with anemia, gave figures of +60 and +50 per cent at about the time the anemia began to develop. The patient who is now living and who has anemia with a leukemic blood picture has had a basal metabolism of +50 to +35 per cent. Six observations* on 4 cases of erythremia with polycythemia have shown an average basal metabolism of +21 per cent, the extremes being +10 and +35 per cent.

Gunderson,[22] at the Huntington Hospital, has indicated that the increased basal metabolism found in myelogenous leukemia may be dependent upon the abnormal blood formation, it being higher the greater the immaturity of the cells in the peripheral blood. On account of the relationship between these two diseases, it is believed that the increased metabolic rate in erythremia is intimately related to the increased active blood formation. Our

* We are indebted to Dr. J. H. Means for some of the metabolic rate determinations.

cases with the highest rates showed greater bone-marrow activity than those with the lower rates. This view, that increase of metabolism is associated with an increased rate of blood formation, can be reconciled with the view given by Isaacs,[21] who suggests that it is dependent upon the liberation of an excess of nuclear material formed in the increased production of red cells.

Blood Destruction and Consideration of Cause of Anemia in Erythremia. In erythremia, the actual levels of the red cells and hemoglobin may vary markedly within a brief period of time, due especially to vasomotor activity. They also may vary markedly in periods of weeks or months, due presumably to variations in the equilibrium between blood formation and blood destruction. That such remissions and relapses may occur is not well recognized. It is important to do so when judging the effect of therapeutic measures.

There is no evidence that the increase of red cells is primarily due to a decreased rate of destruction. One may readily conceive that the organism with polycythemia strives to compensate for the increased blood formation and to remove the excess of blood by increased activity of the process of blood destruction. The development of anemia following polycythemia may be explained on the ground that overcompensation occurs, the hemocidal process becoming excessive so that anemia ensues. The anemia may also be explained as being dependent upon some alteration in the type of blood formation.

There is scant reference in the literature to blood destruction in erythremia. During life an increased output of urobilin has been noted, and microcytosis may be a feature. Thus, some increased blood destruction may at times occur in erythremia; and our observations further support this view. On the average, the 3 cases with anemia appeared slightly sallow. A few isolated observations on their plasma showed it to contain a slight excess of bile pigments. The output of urobilin in the stools was found to be increased to two to three times above normal. These observations, as well as the occurrence of microcytes, suggest that abnormal blood destruction was present.

Experimentally, it has been shown by Krumbhaar and Chanutin[23]

and others that following experimental polycythemia, induced by repeated transfusions of blood, there may develop an anemia with increased number of young red cells in the circulation. There occurs an increased output of urobilin during the stage of polycythemia, and a still greater increase with the development of anemia. Such an experimental condition may appear comparable to the clinical cases referred to. Increased blood destruction may account for the anemia in these animals but, as discussed below, it does not seem to be the chief cause for the anemia in the three individuals referred to above.

It is recognized that the spleen is deeply implicated in the process of blood destruction, and it is attractive to assume that its enlargement in erythremia may be associated with an increased amount of blood destruction. The increase in size of our patients' spleens coincident with the development of the anemia might be considered as dependent upon an increase of hemolysis that produced the anemia. If such was the case one would expect to find at postmortem considerable evidence of blood destruction.

Postmortem observations concerning blood destruction in erythremia are very meagre. It has been reported[8] that increased phagocytosis may occur, but it is evident from a few available reports that this is not the rule. Weber[8] and others believe that the splenic enlargement in polycythemia vera is at least partially due to hyperplasia of the splenic pulp associated with increased hemolysis, and that the enlargement cannot be wholly accounted for by the partial myeloid transformation seen in some cases, or by the presence of erythroblastic foci. Engorgement with blood accounts for some of the enlargement.

The postmortem examination of our cases revealed no unusual amount of phagocytosis in different parts of the body, and there appeared to be no increase of pigment deposit. There was thus no postmortem evidence of excessive blood destruction. However, clinical signs of abnormal blood destruction were obtained, but there was no evidence that this was more than slight. It thus seems distinctly improbable that this patient's progressive anemia was fundamentally dependent upon excessive hemolysis.

The anemia may be explained on the grounds that following

years of an abnormally excessive erythroblastic activity, the response of the marrow succumbed to the strain and became most disorderly with the proliferation of immature leukoblastic and other elements as occurs in myelogenous leukemia. This degenerative proliferation will readily account for the progressive enlargement of the spleen and liver in this individual. However, from reported autopsy observations, as well as from 3 additional cases that Minot has observed post mortem, it seems that the splenic enlargement of many cases of erythremia can be only partially, and sometimes not at all, accounted for by myeloid foci or metaplasia. There is not a complete understanding of the hypertrophy as Weber[8] has indicated.

Another form of altered blood formation other than an embryonic hyperplastic type may account for development of anemia in erythremia. Freund's[24] case suggests that where the cause of the disease permitted at first stimulation, it later was so "toxic" that cessation of blood formation resulted. His case of polycythemia gradually developed the blood picture of pernicious anemia and an aplastic marrow was found postmortem. The effect of antisyphilitic measures may have influenced this patient's marrow.

Excessive irradiation leads to anemia, and one may appropriately wonder if such therapy had produced the anemia in our cases. They had been treated by radium, but it is not believed that radiation enhanced the anemia or caused the leukemic-like blood picture which these patients developed. The increase in the size of the spleen and the distinct drop in the red cell count occurred in the 2 cases that died prior to any radiation. The one that did not come to autopsy showed the further temporary distinct rise in the red cell and hemoglobin level, and this followed four doses, each of about 3000 mc. hours, of radium irradiation over the spleen, given some weeks apart. Only one further radiation treatment was given, this being only 3000 mc. hours, at a time when the count was 3,500,000 per cm., eight months before death. A few radium irradiations of 3000 to 5000 mc. hours were given some months apart to the patient that came to autopsy. These appeared to help the patient symptomatically, but distinct alterations in the blood did not occur except for a tendency to decrease for a

time the numbers of immature bone-marrow cells. The third patient, who is living, received irradiation at least two years prior to the increase in size of the spleen with the development of anemia. During two years prior to this event, relatively small doses of roentgen-ray were given, followed at that time by decrease in the size of the spleen.

Further Consideration of Blood Destruction. Tileston,[22] in his résumé upon hemolytic jaundice, refers to the fact that cases of erythremia in the terminal stage may exhibit a leukemic blood picture and develop an anemia and thus simulate cases of the former disorder. This is certainly true, and though excessive blood destruction does not wholly account for the development of anemia in erythremia, it most probably does so in hemolytic jaundice. However, it does appear from clinical observations alluded to above and from data given below that an increase of blood destruction varying from time to time does occur in erythremia. It is believed that such is the case, because both an increased output of urobilin and an excess of microcytes may occur. Likewise, as referred to later, the alterations in the fragility of the red cells and the hemolytic properties of the serum further support such a view.

In some cases with polycythemia that may or may not be cases of true erythremia, excess of blood destruction seems to account for the development of an anerythremic phase. This is indicated particularly by the report of cases that have shown the features of chronic acquired hemolytic jaundice,[8 26] including increased fragility of the erythrocytes to hypotonic salt solution. We have also observed one case of quite typical hemolytic jaundice, that had some anemia, develop a red count for over a year of about 7,000,000 per cm., with the hemoglobin about 110 per cent. Both the maximal and minimal resistance of the red cells to salt solution remained diminished. This is in contrast to our observations of the fragility in undoubted erythremia reported below, where the minimal resistance was never diminished.

Increases in the output of urobilin are not necessarily dependent upon an excess of blood destruction. Even so, blood destruction is characteristically associated with such an increase. A few iso-

lated reports, such as those of Eppinger and Charnas,[27] Bauman,[28] Giffin *et al.*,[29] Wilbur and Addis,[30] upon the output of urobilin in erythremia are to be found in the literature. None shows a decrease. The majority show some increase, but this is rarely marked. The few estimations that we have made have always shown at least a slight absolute increase.

Twelve determinations of the urobilin output in the stools by the method utilized by Robertson,[31] in 6 cases with the red cells elevated about 7,000,000 per cm., gave 10,000 dilution units as the lowest figure and 27,000 as the highest. (The upper limits of normal are considered 8000 dilution units.) Urobilinogen and urobilin were present in increased amounts in the urine of some of these cases. One observation, a year before death, on the case with anemia that came to autopsy showed the fecal urobilin to be 15,000 dilution units, while an isolated observation on the living case with anemia gave 33,000. Consecutive observations over a long period of time have not been adequately made, though in the case that developed anemia that did not come to autopsy six determinations were made over a period of two years. When the red cell count was about 6,000,000 per cm. there was a urobilin output averaging 18,000 dilution units; with anemia this figure increased, so that when the red count was in the vicinity of 3,500,000 per cm., a figure of 25,000 dilutions was obtained. It is evident, therefore, that the output of urobilin may be essentially no more marked in cases with anemia than when polycythemia is present. Chester M. Jones,[32] in his study of the bile pigment output in the duodenum, has pointed out that, though the actual pigment figures may be above normal, the figures when considered in relation to the red cell count may be below the normal average. Thus, the process of blood destruction in erythremia, as judged by such figures, may be no greater than normal for the number of red cells present. Dr. Jones has kindly determined from the duodenal contents the bile pigment output in 3 of our cases with marked polycythemia. In 1, the average output was 323 dilution units, the normal figure being but little over 100. Urobilinogen was present in an abnormal amount. The other 2 cases showed 220 and 190 dilution units for the average pigment in the duodenal con-

tents. No urobilinogen was present. An analysis of the data suggests that following the time when the highest figures were obtained, the red cells and hemoglobin tended to fall; they at least did not rise, as was the case in some instances when the output of urobilin in relation to the red count was not increased. No definite relationship of the urobilin output to the fragility of the red cells has been determined, though it would appear as if an initial onset of hemolysis in more concentrated salt solution than normal was particularly to be found with distinct increases of the urobilin output. Distinct increase of the urobilin output, however, occurred without such alteration in red cell fragility.

Microcyte formation, particularly when the cells show tailing and signs suggesting fragmentation, may be considered as dependent upon increased blood destruction.[33] We have observed the presence of many microcytes in some instances of erythremia with high counts, while a few such cells are frequently to be observed in the blood of these patients. At times in erythremia no microcytes are observed, while at other times in the same case they appear.

In the cases that developed anemia, microcytes were constantly found, though they never appeared in very excessive numbers, and at times were scant. Thus, fluctuation in microcyte formation occurs in this disease, as does fluctuation in the output of urobilin. The relationship between these two factors cannot be adequately correlated from the data at hand. It is not unreasonable to assume that fluctuation of both microcyte formation and urobilin output indicates alteration in the degree and intensity of blood destruction in this disease. Such an increase may be looked upon as Nature's effort at compensation for the excess of blood, and account for some but not all of the fluctuations that occur in the level of the red cells and hemoglobin.

Fragility of the Red Cells. The influence of the polycythemic process on the red corpuscles is shown by the behavior of these cells when placed in hypotonic sodium chloride solution and in hypotonic blood serum.

A. To Salt Solution: The few reported investigations of the fragility of red corpuscles to salt solutions in erythremia often

show abnormal but varying results which are difficult to reconcile. Normal, increased and decreased, maximal and minimal resistance is reported. The results are chiefly concerned with isolated cases and no very complete studies have been made. Weber,[8] Marsh[20] and some others have recorded the occurrence of a normal fragility, while several have noted increase of fragility, particularly Högler[34] and Gutzeit.[35] Högler[34] reports cases with a slight increased maximal resistance, but with a normal minimal resistance, as well as cases with normal resistance. Gutzeit[35] studied the fragility in 5 cases. He observed combinations of increased maximal and minimal resistance, and increased maximal and decreased minimal resistance. Following radiation, there occurred a decrease of the maximal resistance. His figures show a lengthening of the resistance range. On the other hand, distinct diminution in the fragility of the red cells may occur as reported, for example, by Ward,[36] Isaacs,[21] Bensis[37] and Marsh.[20]

In our series of 15 cases of erythremia, we have noted, also, variations in the fragility of the red corpuscles when tested against hypotonic sodium chloride solutions. The normal values for concentrations of sodium chloride in which hemolysis is first observed and in which it is complete are 0.42 per cent and 0.28 per cent respectively. The upper normal limit for the difference between the per cent salt solution in which initial and complete hemolysis occurs is 0.15. With these figures in mind, we note the following abnormalities:

1. A lengthening of the resistance range (span); that is, a greater than normal difference between the concentration in which hemolysis begins and the concentration in which it is complete.

2. An increased fragility of the red corpuscles; that is, beginning hemolysis in a concentration of sodium chloride definitely greater than 0.42 per cent, with complete hemolysis at the normal point or in weaker salt solution than normal.

3. Complete hemolysis occurring in a concentration of sodium chloride definitely lower than 0.28 per cent, with a normal, increased or decreased initial hemolysis.

4. A "trickling effect," by which we mean a slow onset of hemolysis; a slight, but definite, occurrence of hemolysis in high concen-

trations of sodium chloride, with marked hemolysis occurring in not far from the same concentration as seen in the case of normal cells which normally is close and not far from the very beginning of hemolysis.

These abnormalities are not characteristic of erythremia, but are probably related to alterations in blood production and perhaps blood destruction.

In 40 observations upon 15 cases of erythremia, an increased resistance range was noted in 10 cases. Four cases showed a span of over 0.2, the highest figure recorded being 0.34. In no case was the span abnormally short. Six observations upon 1 case and 5 observations on 2 others over a period of four years showed a tendency for the resistance range to increase from the vicinity of 0.15 to 0.2 or greater as time went by. A definite increase in the concentration of the solution in which initial hemolysis occurred was noted in 6 cases, as shown by 16 tests. This varied between 0.54 per cent and 0.46 per cent, and there was a tendency for the same case to show a similar initial hemolysis in spite of marked variation in the red cell count and hemoglobin. With the increase of initial hemolysis, the complete hemolysis occurred at least at the normal point, and 12 of the tests showed it to be complete in abnormally low concentrations, it being 0.18 per cent in 1 instance and 0.2 per cent in 4 others. Three cases showed a decrease of initial hemolysis, it being 0.38 per cent or 0.36 per cent, complete hemolysis occurring from 0.18 per cent to 0.26 per cent. The "trickling effect" was particularly seen in the cases with increased fragility, though observed in some others.

B. To Dilutions of Sera: In the literature, one finds isolated observations upon the fragility of the red cells by other methods than hypotonic salt solution. For example, Pickard[38] noted increased resistance to antihuman amboceptor, which decreased as the patient's red count dropped, leading him to the conclusion that the anerythremic phase was dependent upon an increase of hemolysis. Lutenbacher[39] and Freund and Rexford[40] each found in 1 instance no hemolytic property of the polycythemic serum. From the results of various tests of fragility of the erythrocytes and allied but incomplete data, several, including Herrneiser,[41]

have deduced hypotheses to suggest that in erythremia increases and decreases of the rate of blood destruction occur. One must recognize that the mechanism of such tests must greatly deviate from the actual state of affairs within the body.

We have investigated also the resistance of the red corpuscles in another way, previously described by one of us.[42] By this method, the resistance of the red corpuscles is tested simultaneously against hypotonic sodium chloride solution, dilutions of the patient's own serum and dilutions of the serum of a normal individual of the same iso-agglutination group. At the same time, the resistance of the normal red corpuscles is tested against dilutions of the patient's serum. With this method, 18 observations have been made on 9 different patients. The outstanding abnormalities shown are of two types, as follows:

1. A tendency toward an abnormally long resistance span in the mixture of patient's cells and patient's serum, and in the mixture of patient's cells and normal serum. Normally, this resistance span in such tests is not over 0.2. In all but 1 case, the resistance span of the patient's cells in dilutions of the patient's serum was, on at least 1 observation, above this figure, and above it in 13 of 18 observations. The greatest span was 0.7, and 7 observations showed it to be between 0.38 and 0.46. There were but 8 tests with patient's cells and normal serum. These showed the span to be distinctly shorter than when the patient's cells were mixed with dilutions of their own serum. There was, however, a tendency for it to be slightly longer than normal by about 0.04. Dilutions of the patient's serum did not alter the resistance span of normal cells.

2. The second form of abnormality noted was a concentration of soluble serum constituents corresponding to an abnormally high concentration of sodium chloride permitting initial hemolysis—that is, increased fragility of the red corpuscles—in the case of mixtures of patient's cells and patient's serum, in the case of patient's cells in normal serum, and in the case of normal cells in patient's serum.

Four of the 9 patients showed on at least one occasion an

increased fragility of their corpuscles when placed in their own serum. When more than 2 tests were made, some months apart, changes from an increased to a decreased fragility were observed, possibly dependent upon therapy, as suggested by Gutzeit.[35]

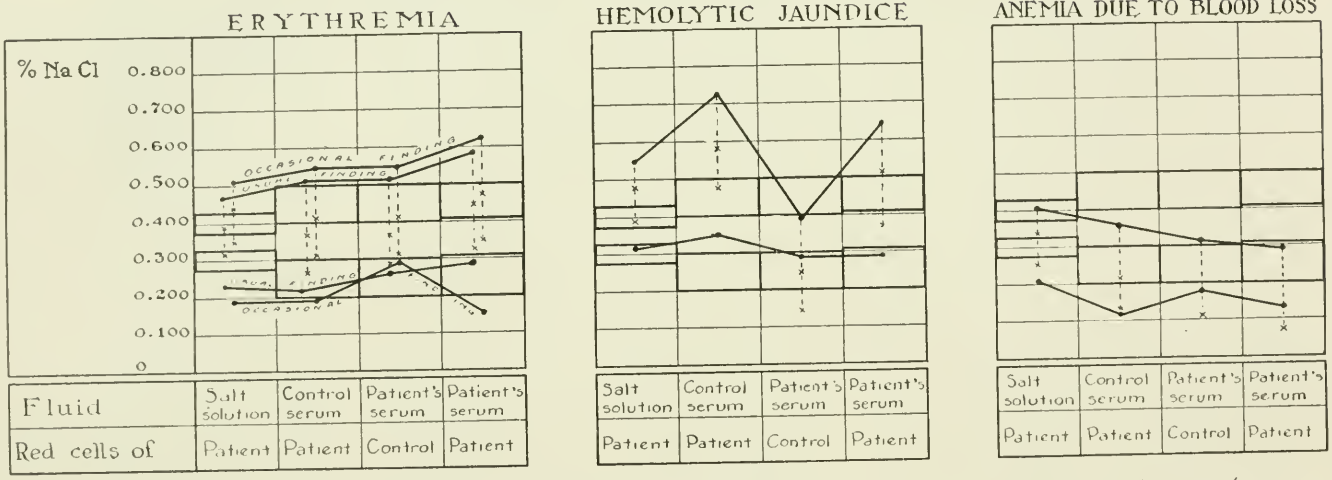
The shift in the dilutions of serum from the normal initial hemolysis of the equivalent of 0.5 per cent sodium chloride was as marked as to begin in 0.9 per cent, though usually in 0.54 per cent to 0.6 per cent. In 2 instances the initial hemolysis was found to be somewhat decreased. When the fragility of the cells was increased in their own serum, it was increased when tested against normal serum. The degree of increase was, however, distinctly not so marked. Six tests were made of normal cells with 6 different patients' sera. They showed a definite tendency to become hemolyzed in a lesser dilution, increased hemolysis, than in their own serum.

These various serum fragility tests did not run parallel with those made with salt solutions. It was true, however, that if the salt fragility test showed increased initial hemolysis or a long resistance span, the test with dilutions of the patient's serum and his own cells showed a similar state of affairs. However, gross alterations in this latter test occurred without alterations in the former.

Chart I with its legend shows examples of the abnormalities referred to above, and contrasts the findings in some cases of hemolytic jaundice and many cases of chronic anemia due to repeated blood loss. The chart does not show an example of the more normal findings that may occur in erythremia, or an instance where the initial hemolysis begins in less concentrated salt solution than normal.

C. Significance of the Fragility Tests: In evaluating the results of these various tests, one naturally first endeavors to associate them either with other laboratory data or a clinical condition of the same patients. Yet our own data and the observations reported in the literature do not seem to warrant the conclusion, at present, that any definite and undoubted relation exists between the clinical condition of the patient or other laboratory

FRAGILITY OF RED CELLS



Heavy rectangles indicate limits of variations in concentrations corresponding to beginning and complete hemolysis in the normal.
On vertical dotted lines, distance from dot on continuous black line to first cross represents minimal normal resistance span; distance to second cross represents maximal normal resistance span.
Dots on continuous heavy lines represent concentrations corresponding to beginning and complete hemolysis in a given case.

CHART I.

The chart shows the alterations in the fragility of the red cells in the usual cases of erythremia as well as an illustration of the most markedly abnormal findings. It does not show the other forms of alterations, nor the fact that normal findings may occur, as noted in the text. A contrast between these findings and those observed in certain cases of hemolytic jaundice and chronic anemia due to repeated blood loss is also shown.

data and the results of various fragility tests. One is forced, for the present, to set forth a hypothesis in order to correlate the findings.

It is to be recollected that alterations in red cell fragility may be due to a variety of causes. Changes in the carbon-dioxide content of the blood may produce alterations as noted by Stadie and Van Slyke,[43] and by Greenthal and O'Donnell.[44] The fluctuations following exercise noted by Libermann and Acel[45] might be due to such a cause, or might be dependent upon changes in the destruction of cells which may occur following exercise, as noted by Broun.[46] It would seem as if, besides the direct influence of chemical substances on the fragility, fundamental changes in the character of the cells dependent upon their manner of production or destruction would affect their resistance.

However, as Rous[33] has pointed out, many investigators have attempted to show that alteration of the fragility of the red cells gives an indication of their age, although others have been unable to bring forth any evidence to substantiate this theory. There is no available means of determining the relative age of erythrocytes, except in the case of relatively very young ones. Some believe increased fragility is dependent upon an excess of mature cells, while others, as Meulengracht,[47] believe this is a sign of youth. From the statements made below, together with such studies as those of Rusznyák and Barát[48] and Schustrow and Wlados,[49] it is probable that increased resistance, especially the maximal, is affiliated with immature cells.

One must be impressed with the constancy of the results of fragility tests performed on normal red cells; likewise with the fact that the resistance span becomes shorter than normal[42 50 51] in cases in which the bone-marrow shows fatty aplasia and thus ceases to discharge cells into the circulation; and hence in cases in which presumably the red cells tend to approach the same age.

Moreover, there has been noted[52] a distinct tendency to a lengthening of the resistance span, with particularly a diminution of the point at which complete hemolysis occurred in salt solution in cases of prolonged chronic anemia, due to blood loss, as well as from other known causes in which distinct hyperplasia of marrow

occurs. Slight decrease in initial hemolysis usually occurred. Similar results[52] have been obtained in rabbits following experimental chronic anemia due to blood loss. In spite of the fact that Pepper and Peet[53] and Key[54] have considered that reticulated cells are neither more nor less fragile than adult cells, it has seemed to us from certain observations concerning the effect of solutions upon reticulated cells observed under the microscope that they may be more resistant than adult cells. It is not intended to give here a full discussion regarding the production of cells and their fragility. It, however, has seemed to us from what has been said above, together with a careful consideration of much literature, that an increased resistance span, and particularly an increase of the maximal resistance (less concentrated salt solution), is associated with an active hyperplastic marrow, which probably permits cells of many ages to appear in the circulation, particularly immature ones, though not necessarily immature enough to show reticulation.

In erythremia the peripheral blood contains cells of a wider age range than normal, at least during certain phases of the disease, as shown by histological studies. This, perhaps, may be further manifested by the increased length of the resistance span. The concentration of salt in which initially complete hemolysis occurs may quite possibly shift upward or downward respectively according to whether there is a preponderance of old or young cells present.

The increase of initial hemolysis (increase of fragility) may be dependent upon the numbers of old cells that are present. The "trickling effect" might indicate the presence of excessive numbers of old cells in the blood, the bulk of the cells being of the same mean age as are those of a normal individual. An increased fragility is often associated with conditions in which undoubted alterations in blood destruction occur, chronic hemolytic jaundice being the classical example. There is only indirect evidence that increased fragility may be due to excessively old or a predominance of old red cells, while there is some evidence at hand, as given by Pearce,[55] to suggest that their diminished resistance is related to increased hemolysis due to an augmentation of splenic activity. The recent observations of Bolt and Heeres[56] further

indicate that the spleen has the power of diminishing the osmotic resistance of the erythrocytes, as shown by testing blood before and after coming in contact with it. This organ, as well as others, may prepare cells for hemolysis, as suggested long ago by Bottazzi;[57] cells so affected when tested by different methods may break up with greater ease than normal. Increased hemocidal properties of the serum are not necessarily to be found if one recognizes that the cell may be prepared for hemolysis by the action of an organ. It thus seems not unreasonable to assume that increase of the concentration, in which initial hemolysis occurs with or without decrease of the point of complete hemolysis, is dependent upon all or some of the cells in the body having been subjected to the influence of a hemolytic process. With this variation, the resistance span not only may be lengthened if cells of widely different ages are present, but also may be in an abnormal range, as occurs in hemolytic jaundice. In such a disease, alterations of fragility might depend upon a pathologically formed cell.

Thus, the point of view is offered that increase of fragility is especially dependent upon cells that have been damaged in some manner, as by a hemolytic process, and that decrease of hemolysis, especially the point of complete hemolysis, is associated with some form of immature cells, not necessarily reticulated. A predominance of old cells may influence the character of the result of a fragility test, and a long span is indicative of the presence of cells of many ages.

It is thus possible that a patient with erythremia may show a normal resistance span within normal limits or any of the variations mentioned above, depending upon the state of balance between the rate of delivery of relatively young cells to the blood and the rate or method of removal of cells.

Our data also bring out another point: That humoral factors may play an important part in blood destruction in erythremia. As indicated, normal red corpuscles begin to hemolyze at higher concentrations when mixed with the serum of some patients suffering from erythremia than they do when mixed with the serum of a normal person. The serum appears to exert a hemolytic influence on the red cells. The same is reported by Buckman and Horrall[58]

in the case of serum from persons suffering from pernicious anemia and Streptococcus hemolyticus septicemia. This is in sharp contrast to the results obtained in certain cases of hemolytic jaundice, where the sera behave normally, and in certain cases of anemia following blood loss, where it appears that the serum develops a sparing influence on the red cells. It is interesting to note, too, that although there is usually an increased resistance span in the case of mixtures of the erythremic patient's cells and serum, this span approaches normal dimensions in the case of normal cells tested against the serum of patients suffering with erythremia, even though hemolysis does tend to begin at a high concentration.

Presumably, one is dealing with two opposing factors: Increased production of red corpuscles tending to flood the blood with cells, which if not destroyed would inevitably result in the presence of an increased number of cells of all ages, and at the same time a compensatory hemolytic process tending to destroy the red cells. As a result of the former, one would expect a lengthened resistance span with hemolysis being complete in a relatively low concentration (due to young cells), and perhaps beginning at a relatively high concentration, due to a sufficient number of old cells. A hemolytic influence, as that of the spleen, might cause an increase of initial hemolysis to be observed with or without augmented hemocidal activity of the serum. So far as is known, there is no evidence to contradict such an explanation and the data at hand in part substantiate it.

Summary. 1. Certain aspects of erythremia are presented from a study of 15 cases.

2. The increased activity of the marrow in erythremia is reflected in the peripheral blood by increases of all three formed elements originating from it—erythrocytes, leukocytes and platelets. It is evidenced likewise by the appearance of abnormal and immature forms of all three elements, which may occur in greatly augmented numbers. The blood picture may then resemble that of myelogenous leukemia.

3. Three cases are recorded that, after having polycythemia for many years, developed anemia, coincident with a further increase

in the size of the spleen and a leukemic blood picture. One of these cases was examined post mortem. The spleen, liver and bone-marrow showed a hyperplastic blood formation very similar to that seen in myelogenous leukemia.

4. Myelogenous leukemia and erythremia appear intimately related, and both may be of a neoplastic nature. There occur cases of erythremia and leukemia that illustrate multiple varieties of varying degrees of primary pathological activity of the myeloid tissue, which usually conforms to a definite type.

5. The basal metabolism is often increased in erythremia. The increase is believed to be affiliated with the augmented activity of blood formation, as it is in myelogenous leukemia.

6. The development of marked anemia in erythremia, as in leukemia, is dependent upon a disorderly proliferation of the myeloid tissue.

7. In erythremia, some increase in the output of urobilin is the rule and commonly microcytes occur in the blood. These findings, as well as perhaps alterations of the serum and red cell fragility, suggest that increased blood destruction takes place, though post-mortem studies seldom reveal signs of such a process.

8. Some of the fluctuations in the level of the red cells and hemoglobin probably depend upon variations in the balance between blood destruction and blood formation.

9. The influence of the polycythemic process on the red corpuscles is evidenced by the deportment of these cells when placed in hypotonic sodium chloride solution and in hypotonic blood serum. These tests show the abnormalities indicated below, but do not give necessarily parallel results.

(*a*) A lengthening of the resistance range is often observed.

(*b*) An increased, normal or decreased initial hemolysis (point of minimal resistance) may occur.

(*c*) Complete hemolysis (point of maximal resistance) never occurs in more concentrated solutions than normal. It often takes place in much less concentrated solutions than normal.

(*d*) Patients' cells in dilutions of their own or normal serum may yield an abnormally long resistance span and may break up in a dilution of an equivalent of a stronger concentration of sodium chloride than normal.

(*e*) Normal cells may hemolyze in dilutions of patients' serum more readily than in their own. The resistance range in either serum is less than that of erythremic cells.

Hence the erythremic serum may exert a hemolytic influence on red corpuscles; in a case of erythremia, some of the cells may be more vulnerable than normal and others distinctly less so.

10. It is suggested that a lengthened resistance span in fragility tests is due to cells of a greater age variety than normal; that an increase of resistance, especially the maximal resistance, is dependent upon an increase of some form of immature cells; and that decrease of minimal resistance is indicative of some hemocidal influence on the cells, or perhaps due to a relatively large number of old or pathological cells.

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THE TREATMENT BY SPLENECTOMY OF ESSENTIAL THROMBOCYTOPENIA (PURPURA HEMORRHAGICA)*

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The role of the blood platelets in hemopholia and purpura hemorrhagica, which comprise the hemorrhagic diseases, is of paramount importance. Hemophilia is the result of some qualitative change in the blood platelets (Fonio,[1] Minot and Lee[2]) resulting in defective coagulation of the blood. Purpura hemorrhagica is accompanied by a qualitative change and by a greatly diminished number of blood platelets, and also some change in the capillary activity resulting in a hemorrhagic tendency. This constant diminution of the platelets without any known cause (Denys,[3] Hayem[4]) has given rise to the better modern name of essential thrombopenia (Frank[5]) or better still thrombocytopenia (Eppinger[6]). Essential thrombocytopenia is a distinct clinical entity and is characterized by the following main features:

1. Diminution of the Blood Platelets: The average number of blood platelets in normal blood is 250,000. The platelets vary from none to 100,000 in this disease; at times the number may reach the normal figure. Hemorrhagic manifestations come into evidence when they fall below 60,000.
2. Preservation of normal Coagulation Time of the venous blood.
3. Prolongation of Bleeding Time (Duke[7]): Puncture of the lobe of

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the ear is followed by some oozing of blood for one to three minutes normally. In thrombocytopenia this is prolonged usually from ten minutes to hours.

4. Positive Capillary Resistance Test (Hess[8]): A tourniquet applied to the arm sufficient to prevent the return circulation without obliterating the pulse is followed by a shower of petechiæ.

5. Failure of Clot Retraction (Hayem[9]): Clot retraction does not occur before splenectomy in this disease even when the blood platelets increase to 80,000. In a few obscure cases the blood platelets may be normal in number without clot retraction, but accompanied by the other characteristics of essential thrombocytopenia, such as a prolonged bleeding time and positive capillary resistance test. Glanzmann[10] has attributed this condition to some defect of the blood platelets and has called this condition thrombasthenia.

The clinical manifestations of thrombocytopenia are:

1. Acute or Chronic Course: The acute may get well, run a short fatal course or become chronic. The chronic condition, as a rule, appears in young individuals, usually girls.

2. Apparently Spontaneous Hemorrhages into the skin and from mucous membranes, which may be continuous or intermittent.

3. Excessive Hemorrhage from Slight Trauma: The outcome is usually, in weakness and physical incapacity, due to a severe grade of anemia following the intermittent attacks of hemorrhage. Death not infrequently occurs from exsanguination.

Pathogenesis. Capillary hemorrhage is normally stopped by the production of a small blood platelet thrombus and by the inherent contractility of the vessels. The thrombus results from the adhesion and rapid agglutination of the blood platelets in the opening of the vessel from which the blood is oozing. The thrombus acts like a dam and prevents further bleeding.

One of the normal functions of the circulating blood platelets is to prevent the diapedeses of the red blood cells between the endothelial cells of the capillaries (Frank[11]). There is also some proof that the blood platelets participate in the control of vascular contractility (O'Connor,[12] Janeway[13]); this contractility also reënforces the protective mechanism against capillary hemorrhage.

Any disturbance in the production or of the function of the blood platelets brings about a bleeding tendency due to the subsequent effect on the activity of the capillaries. The slightest trauma to the body then becomes evident by the appearance of hemorrhages often uncontrollable. An examination of the blood during such a period in a case of essential thrombocytopenia will reveal the marked diminution of the blood platelets, usually below 100,000 per cmm. and occasionally as low as 50. We have never observed their complete disappearance when they are counted directly in undiluted citrated plasma. In the intermittent type of thrombocytopenia the hemorrhagic tendency becomes evident when the number of blood platelets fall below 10,000 or less. Clot retraction is usually absent even when the blood platelets are as high as 80,000. There is a certain parallelism between the bleeding time, capillary resistance test and the number of blood platelets.

Concerning the cause of the thrombocytopenia there are two main theories:

1. Diminished production of the blood platelets as a result of some toxic or inhibitory action of the spleen on the megakaryocytes of the bone marrow which, according to Wright,[14] are the mother cells of the blood platelets. This theory, proposed by Frank,[5] led to the treatment of chronic thrombocytopenia by means of splenectomy.[2]

2. In such cases, Kaznelson[15] found no diminution of the megakaryocytes in the bone marrow. He frequently noticed enlargement of the spleen and came to the conclusion that an increased function on the part of this organ in the destruction of blood platelets was responsible for their diminution in the blood. Kaznelson[16] was the first to apply this knowledge and have a splenectomy performed in a case of chronic thrombocytopenia. The spleen of this case showed the presence of numerous large blood platelets. He suggested the name thrombolytic purpura for the condition. We shall discuss the validity of these theories later.

Splenectomy for Essential Thrombocytopenia. The exceptionally good results from splenectomy reported by Kaznelson[17] soon made the procedure the method of choice as a remedial or life-saving measure in this disease when all other therapy has failed. So

far 17 cases of essential thrombocytopenia (including 2 reported in this paper) have been treated by splenectomy. (See Table I.)

TABLE I.—CASES TREATED BY SPLENECTOMY FOR ESSENTIAL THROMBOCYTOPENIA

Case No.	Date.	Author.	Result.
1	1916	Kaznelson [16 17]	Well.
2	1916	Kaznelson[16 17]	Well.
3	1916	Kaznelson[16 17]	Greatly improved.
4	1917	Benecke[18]	Well.
5	1917	Schmidt[19]	Well.
6	1917	Schmidt[19]	Greatly improved.
7	1919	Minkowski[20]	Greatly improved.
8	1920	Ehrenberg[21]	Well.
9	1921	Eylenburg[22]	Well.
10	1921	Kaznelson[23]	Died.
11	1921	Kaznelson[23]	Well.
12	1921	Minot[23]*	Well?
13	1922	Cori[24]	Well.
14	1922	Steinbrinck[25]	Greatly improved.
15	1923	Bowen[26]	Well.
16	1923	Brill and Rosenthal	Well.
17	1923	Brill and Rosenthal	Well.

The postoperative course in all the successful cases was about the same. The following points are noteworthy:

1. Blood-platelet Crisis: The increase varied from 25,000 to 1,500,000.

2. Immediate Cessation of the Hemorrhagic Tendency: In a few cases the tendency recurred but not as severely as formerly.

3. Later Return of the Blood Platelets to Their Previous Low Level: This took place from a few days to a few weeks after the splenectomy.

4. Increase of the hemoglobin and the red blood cells.

5. Apparent cure of the condition.

The remarkable results reported from splenectomy led us to undertake this procedure in 2 cases of essential thrombocytopenia in which all known methods of treatment, especially transfusion, failed. Both cases were in a very serious condition and were almost moribund. Splenectomy brought about immediate improvement and apparent ultimate cure, and undoubtedly acted at the time of operation as a life-saving measure:

*Quoted by Kaznelson.

Case I.—R. G., chronic essential thrombocytopenia (purpura hemorrhagica); splenectomy; recovery.

Girl, aged nineteen years. Admitted to the First Medical Service, Mount Sinai Hospital, October 26, 1922, complaining of uncontrollable bleeding from the nose, mouth and stomach.

Family history and past history were negative. No bleeders in the family.

Present Illness. The patient was perfectly well until five years of age, when she had an attack of "kidney trouble" (bloody urine and generalized edema). This was followed a few weeks later by an uncontrollable nasal hemorrhage, for which the child had to be taken to a hospital, where she remained for five weeks.

Since then, about once each year, the patient has had an attack of severe bleeding from nose and mouth and vomiting of blood. During the attacks she became very weak and pale. The bleeding continued on and off, lasting from one to five days, occasionally longer. In the interval between attacks the patient usually felt quite well. However, she always noticed black and blue spots on her skin; these occurred from the slightest trauma. The menses during an attack were usually repressed. Lately the periods have been greatly prolonged.

The present attack began three days before admission, after the patient had been apparently well for two years. The bleeding has been going on and off from the nose and mouth. Some of the blood coming down from the back of the nose is swallowed and then vomited.

Eight transfusions have been given within the past eight years without producing any lasting effect.

Physical Examination. General Condition. Fairly well-nourished and well-developed girl, acutely ill. Marked pallor of face. Vomiting dark red blood repeatedly.

Mouth: Pyorrhea. Gums somewhat spongy but not bleeding. Blood-clots seen in pharynx.

Neck: Bilateral adenopathy.

Heart: Loud blowing systolic murmur at apex; not transmitted.

Abdomen: Liver not palpable.

Spleen: Felt 1 cm. below the costal margin.

Extremities: Slight pretibial edema. Old scars and pigmented areas.

Skin: Widely distributed hemorrhagic areas varying in size from a petechia to a large ecchymosis. These areas are most marked on the legs and confluent.

Progress of case.

Oct. 26, 1922. Direct transfusion (Unger method) 600 cc. There was no bleeding for five days following this transfusion. A distinct increase in the size of the spleen was noted 3 cm. below the costal margin.

Oct. 30. Blood examination: Hemoglobin, 38 per cent (Kuttner); Red cells, 2,272,000; White cells, 6800; Platelets, 6400; Differential, 300 cells counted; Polynuclear neurtrophils, 54.3 per cent; Polynuclear eosinophils, 1.6 per cent; Polynuclear basophils, 2.0 per cent; Myelocytes, neutrophilic, 1.3 per cent; Lymphocytes, 25.6 per cent; Plasma cells, 2.0 per cent; Monocytes, 13.0 per cent; Normoblasts, 1 per 300 white cells; Coagulation time of blood, ten minutes (test tube); Bleeding time, profuse at end of ten minutes; Capillary resistance test, positive within two minutes; Clot retraction, none.

Opinion: Secondary anemia; essential thrombocytopenia.

Nov. 2 to Nov. 5. Repeated vomiting of old and fresh blood.

Upon examination of the throat, bright red blood was seen issuing from the nasopharynx.

Nov. 5. Hemoglobin, 27 per cent. Direct transfusion (Unger method), 500 cc.

Nov. 9. Slight epistaxis this morning. Vomited blood once.

Nov. 13 to Nov. 15. Slight epistaxis and vomiting blood off and on.

Nov. 15. Twenty cc of horse serum given intramuscularly without effect.

Nov. 16. Hemoglobin, 32 per cent. Direct transfusion (Unger method), 750 cc. No reaction.

Nov. 19. Hemoglobin, 43 per cent. Again vomiting blood.

Nov. 20 to Nov. 25. During this period patient vomited blood repeatedly. During the later hemorrhages the pulse was so rapid that it was almost impossible to count. Pulse otherwise varied from 120 to 140. Pallor very marked. Eyes large and stary at times. Very restless.

Nov. 26. Direct transfusion (Unger method), 500 cc.

Nov. 27. Hemoglobin, 35 per cent. General condition very poor, pallor still marked, expression anxious. Slight epistaxis. Vomited once today. Most of the veins of the forearms are tender and cord-like, evidently due to intravascular clotting, making the transfusions difficult.

Splenectomy to be tried after the next transfusion, which is to be given to improve the patient's general condition.

Dec. 1. Direct transfusion (Unger method), 500 cc.

The transfusion had to be stopped at this point because the patient complained of severe precordial pain.

Dec. 2. Hemoglobin, 43 per cent.

Dec. 2. Splenectomy by Dr. A. A. Berg.

A greatly enlarged spleen was delivered through a subcostal incision. The wound bled considerably. As soon as the pedicle was clamped all bleeding stopped. There was some oozing from the nose throughout the anesthesia; this also stopped as soon as the spleen was removed. A direct transfusion of 800 cc was given immediately after the operation.

The postoperative recovery was uneventful. The wound healed by primary union.

Summary of Report by Dr. F. S. Mandlebaum. Macro-specimen consists of a large spleen weighing 1400 gm. and measuring 23 x 13 x 6½ cm. Surface is smooth with occasional indentation. Few adhesions on mesial aspect. Vessels patent and not sclerotic. Spleen feels elastic and cuts very easily. Cut surface shows the presence of numerous large follicles. Pulp present in normal amount. Sinuses not dilated or sclerosed.

Microscopically the spleen shows myeloid metaplasia, hypertrophy of the Malpighian bodies. No blood platelets or thrombi.

Dec. 2. Six hours after the operation crops of fresh petechiæ appeared over the upper part of the left chest and the left cheek. All bleeding from the mucous membranes stopped. The hemoglobin rose to 70 per cent.

Progress of case following splenectomy, Dec. 2, 1922 to April 10, 1923.

1. General Condition: Steady improvement; color gradually returned; cheeks and lips are now red. Patient feels perfectly well.

2. Nose and Mouth: Cessation of all hemorrhage from nose. For a short period after the splenectomy there was slight bleeding from the gums but none since.

3. Vomited three times after the operation, but there was no blood in the vomitus. Vomited slight amount of blood only once later.

4. Skin: Petechiæ appeared about six hours after the operation, but none since. All the hemorrhagic areas disappeared. Does not get black and blue marks as formerly. Recently the patient "turned" her knee-cap, but only a slight skin hemorrhage developed.

5. Urobilin and Urobilinogen: Before operation: urine, urobilin test gave marked reaction. After operation: urine, urobilin very faint trace.

6. Blood changes following splenectomy (see Table II).

(*a*) The two transfusions 500 cc given the day before the operation and 800 cc given immediately after the operation raised the hemoglobin to 70 per cent and the red cells to 4,352,000. The following month the hemoglobin fluctuated between 60 and 80 and then rose to 90 per cent. The red cells also followed the high percentage and later rose to 5,864,000. Four months later the hemoglobin again fell to 80 per cent, but the red cells remained over five and a half million.

(*b*) The leukocytes increased to 56,000, but gradually assumed their normal number (5600 to 7000) and later fluctuated between 8000 to 28,000. After the postoperative polynucleosis there followed a persistent monocytosis.

(*c*) The blood platelets showed the usual behavior as in other splenectomized cases of thrombocytopenia. Six hours after the operation 95,000 platelets were present. The following day they rose to 225,000 and again rose on the second day postoperative to 295,000. Then within a week the

TABLE II.—CASE I.—R. G. BLOOD EXAMINATIONS FOLLOWING SPLENECTOMY, DECEMBER, 2, 1922

	Hemoglobin. Per cent.	Red blood cells.	White blood cells.	Platelets.	Polynuclears neutrophiles. Per cent.	Lymphocytes. Per cent.	Monocytes. Per cent.	Coagulation. time.	Bleeding time.	Capillary resistance test.	Clot retraction.
After 6 hours*	70	4,352,000	56,000	95,000	97.0	0.3	2.3	....	1½ min.		
Dec. 3, 1922	66	4,144,000	40,000	225,000	93.3	2.0	4.6	....	2 min.		
4, 1922	68	4,064,000	39,200	295,000	87.6	3.0	9.3	....	1 min.		
5, 1922	60	3,872,000	16,000	220,000	73.6	13.0	12.6	....	2 min.		
6, 1922	62	3,952,000	14,400	270,000	86.0	8.6	5.3	....	1½ min.		
8, 1922	63	3,880,000	15,800	145,000	85.0	8.0	5.0	....	2 min.	Negative	
9, 1922	66	4,160,000	15,000	240,000	74.0	13.6	8.6				
11, 1922	75	4,544,000	7,000	60,000	63.0	18.3	15.3	....	4 min.		
12, 1922	75	4,480,000	7,000	25,000	46.6	31.0	17.0	....	3 min.		
13, 1922	72	4,520,000	6,800	5,000	60.0	24.0	13.3	....	8 min.		
15, 1922	71	4,488,000	8,900	30,000	50.6	24.3	20.3	....	2 min.	Negative	
16, 1922	70	4,960,000	10,000	3,000	66.6	14.0	18.3	....	5 min.		
17, 1922	72	5,120,000	9,600	5,000	44.3	32.3	12.0	....	4 min.		
19, 1922	77	4,832,000	10,600	4,800	65.3	17.6	12.0	10 min.	3 min.	Negative	Very slight.
22, 1922	68	4,480,000	9,000	6,000	62.3	26.6	7.3	....	2 min.		
24, 1922	76	4,736,000	12,200	3,000	56.6	28.0	12.0	....	2 min.		
26, 1922	74	4,800,000	10,200	4,000	61.0	28.3	9.0	....	2 min.		
28, 1922	82	5,200,000	12,400	7,500	53.3	32.0	12.3	....	1½ min.		
Jan. 1, 1923	74	4,576,000	10,200	10,000	59.0	30.3	9.6	....	2 min.		
5, 1923	71	4,512,000	7,800	5,000	31.6	47.0	10.6	....	½ min.		
9, 1923	70	4,120,000	12,000	4,000	45.3	32.6	17.6	....	9 min.	Negative	
13, 1923	80	5,120,000	11,600	10,000	48.6	42.3	6.3	....	½ min.		
17, 1923	80	5,632,000	16,000	6,000	54.0	36.6	9.0				
24, 1923	76	4,736,000	12,800	8,000	57.3	33.3	7.6	....	0		
27, 1923	87	5,376,000	13,800	10,000	52.6	36.6	10.3	11 min.	3 min.	Negative	None.
31, 1923	87	5,440,000	28,000	14,000	51.0	39.0	19.3				
Feb. 3, 1923	80	5,564,000	19,800	16,000	53.3	36.6	9.0				
10, 1923	90	5,864,000	11,200	12,000	54.0	38.0	6.3				
13, 1923	92	6,194,000	12,400	12,000	57.0	36.6	5.3	8 min.	3 min.	Slightly positive	Present.
Apr. 24, 1923	84	6,656,000	14,200	20,000	62.6	26.3	9.6	6 min.	4½ min.	Negative	Present.

* Following two transfusions.

platelets dropped to 5000. After this the bleeding time was usually normal. Occasionally it was prolonged. The blood platelets were distinctly larger than normal ones.

(*d*) The Capillary Resistance Test: This test was usually negative. On one occasion a few petechiæ appeared at the bend of the elbow.

(*e*) Clot Retraction: Very slight clot retraction was present the first month. During the second month no clot retraction. Clot retraction appeared again the third month, but this was somewhat less than normal. Clot retraction was present at a recent examination (April 24, 1923).

Summary of Case. Essential thrombocytopenia (purpura hemorrhagica) of fourteen years' duration with chronic intermittent course. The patient became exsanguinated several times and was transfused as many times with only temporary success. All agents known to stop hemorrhage were of no avail until splenectomy was performed, following which no further bleeding took place. The patient was discharged apparently well. The hemorrhagic tendency has stopped.

Case II.—Chronic essential thrombocytopenia (purpura hemorrhagica); splenectomy; recovery.

Boy, aged fifteen years, admitted to the First Medical Service, Mt. Sinai Hospital, November 22, 1922, complaining of bleeding from the nose and vomiting blood.

Family history and past history negative. No bleeders in the family.

Present Illness. Onset April, 1919 (aged eleven years), when the patient had an attack of tonsillitis followed by hemorrhages into the skin, bleeding from the gums, painful joints, vomiting and pain in the upper part of the abdomen. Also had irritability of the eyes, weakness, fever, chills and sweats. Remained in the hospital for one month. Was apparently well except for an occasional ecchymosis following some slight trauma until May, 1922, when he received a blow on the nose. This was followed by a severe epistaxis which continued for several hours. The bleeding was stopped by means of a tampon saturated with fresh normal blood. The skin hemorrhages had become more frequent since. In July, 1922, while drinking some milk, blood began to issue from the anterior and posterior nares, and soon the patient vomited blood and food. Some hemorrhagic areas again appeared on the skin; *x*-ray therapy was applied to splenic region with apparently good result. His condition improved. He lived a quiet sort of life until the day of his recent admission to the hospital, November 22, 1922, when he was again struck on the nose and has been bleeding and vomiting blood ever since.

Physical Examination. Well-developed and fairly well-nourished boy with marked pallor. Appears acutely ill.

Eyes: Few petechiæ in conjunctivæ of both lower lids.

Mouth: Teeth fair; gums spongy and bleeding; tonsils large and covered with hemorrhagic spots.

Heart: Not enlarged; systolic thrill and murmur at apex.

Spleen: Not palpable but is large to percussion.

Skin: Numerous petechiæ over back, chest, abdomen, thighs and legs.

Nov. 26, 1922. Blood count: Hemoglobin, 45 per cent; Red cells, 2,584,000; White cells, 10,000; Platelets, 10,000 (plasma); Polynuclear neutrophiles, 71.6 per cent; Polynuclear eosinophils, 1.6 per cent; Polynuclear basophils, 0.3 per cent; Lymphocytes, 15.3 per cent; Monocytes, 11. per cent; Cogulation time of blood, ten minutes; Bleeding time, four and a half minutes; Capillary resistance test, slightly positive; Clot retraction, none.

Opinion: Secondary anemia, thrombocytopenia and monocytosis. Blood picture is characteristic of essential thrombocytopenia.

November 29. No further hemorrhages. Petechiæ on legs are gone. Spleen not palpable.

Dec. 2. Epistaxis off and on all day.

Dec. 6. Hemoglobin gradually falling, now 28 per cent. Still bleeds daily from nares. Platelets, 8000.

Dec. 9. Gums spongy and bleeding. Condition getting worse. Bleeding from nose stopped.

Dec. 12. Slight bleeding from gums continues. Marked pallor and weakness.

Blood examination (see Table IV) today shows the following: Hemoglobin, 28 per cent; Red cells, 2,204,000; Platelets, 400; Bleeding time and coagulation time are normal The capillary resistance test is negative, but there is no clot retraction.

Dec. 16. Patient vomited about 7 ounces of dark, clotted blood. Blood seen trickling down from the posterior nares.

Dec. 17, at 12.50 A.M. Bleeding both from anterior and posterior nares. Thromboplastin and adrenalin do not control bleeding. Tampon was not tolerated. Twenty cc of unmodified blood was injected intramuscularly and 10 cc injected slowly into the nose, which arrested the bleeding. Hemoglobin, 30 per cent. Early this morning (4 A.M.) the patient again began to bleed from the nose. Pulse rapid, 140; later (6.30 A.M.), 150.

Hemoglobin, 29 per cent; platelets, 300 (plasma).

Direct transfusion (Unger method), 500 cc.

Dec. 18. No bleeding since transfusion. Slight rise in temperature to 102.8°. Hemoglobin, 38 per cent; Red cells, 2,634,000; White cells, 19,400.; Polynuclear neutrophils, 91 per cent; Lymphocytes, 7 per cent;

Monocytes, 2 per cent; Platelets, 27,500; Bleeding time, thirteen minutes; Coagulation time, eight minutes; Capillary resistance test, negative; Clot retraction, none.

Dec. 19. Crop of new petechiæ on all extremities.

Dec. 22. Edema of uvula and tonsils—traumatic.

Dec. 23. Hemoglobin, 28 per cent; Red cells, 2,010,000; Platelets, 24,000.

Dec. 25 to Dec. 29. Fresh petechiæ appeared daily. General condition getting worse. Pallor and weakness marked.

Dec. 29. Splenectomy decided upon for the relief of the condition. Direct transfusion (Unger method), 450 cc. Severe reaction following transfusion; chill with rise of temperature to 105°.

Dec. 30. Splenectomy performed by Dr. E. Beer through a subcostal incision. Profuse oozing of wound. Continuous oozing from nose during the anesthesia. Soft, slightly enlarged spleen with omental adhesions between stomach and hilus. The adhesions doubly divided and cut. Spleen delivered with some difficulty. Hilus ligated and cut, taking especial care not to include adherent stomach.

Summary of Pathological Report by Dr. F. S. Mandlebaum. Macro-specimen consists of moderately enlarged spleen weighing 300 gm. and measuring 14 x 7½ x 3 cm. It is elastic and cuts easily. Malpighian bodies visible. Microscopic examination only shows hypertrophy. No blood platelets found.

Immediately after the removal of the spleen all oozing of blood stopped from wound and nose. The same effect was noted for the bleeding time as in previous case.

Bleeding time before splenectomy, profuse at the end of six minutes, when it was stopped.

Bleeding time during manipulation at hilus, six minutes; immediately after splenectomy, three minutes; two hours after splenectomy, three minutes; eight hours after splenectomy, three minutes. Bleeding time fifteen hours after splenectomy, two and a half minutes. (See Table III and IV for the blood examinations before and after splenectomy.)

Dec. 31. Blood-pressure: Systolic, 95; diastolic, 70. Pulse, 160; later 132.

Digifolin minims 15 every three hours and Murphy drip two hours on and two hours off given.

Jan. 1, 1923. General condition much improved. Slight abdominal pain, especially in wound and also slight precordial pain. No bleeding.

Jan. 2. Slight nosebleed once during the night.

Jan. 3. Nosebleed once today.

Jan. 4. Slight bleeding again from nose; just a few drops of blood ooze out and stops immediately, never oppressive or profuse as on previous occasions.

Jan. 7. Slight serosanguineous discharge from wound.

TABLE III.—CASE II.—BLOOD EXAMINATIONS BEFORE SPLENECTOMY

	May 5, 1919.	May 1, 1922.	Nov. 26, 1922.	Dec. 18, 1922.	Dec. 30, 1922.
Hemoglobin	70%	78%	45%	38%	48%*
Red cells	3,960,000	4,800,000	2,584,000	2,634,000	2,896,000
White cells	23,000	14,300	10,000	19,400	22,000
Platelets	80,000	80,000	10,000	24,000	None
Polynuclear neutrophiles	83%	63.5%	71.6%	91%	72.3%
Lymphocytes	13%	27.5%	15.3%	7%	14.3%
Monocytes	4%	7.5%	11.0%	2%	6.3%
Coagulation time	5 min.	13 min.	10 min.	8 min.	4 min.
Bleeding time	7 min.	16 min.	4½ min.	13 min.	Profuse at end of six min.
Capillary resistance test	Slightly positive	Slightly positive	Slightly positive	Positive	Slightly positive
Clot retraction	None	None	None	None	None

Jan. 8. Sutures removed, accompanied by bleeding easily controlled with adrenalin.

Jan. 11. All sutures out. Slight bleeding from wound not controlled by thromboplastin. Adrenalin controls the bleeding more satisfactorily. Slight nosebleed. Stopped with adrenalin.

Jan. 19. Patient out of bed. Many petechiæ appeared on legs, few on right lower conjunctivæ.

Feb. 3. Few petechiæ on face and lower legs appear from time to time; gums have entirely improved; no sponginess and no bleeding.

Feb. 8. Hypostatic petechiæ on legs only. General condition excellent. Hemoglobin has risen up to 76 per cent.

Feb. 14. Today for the first time clot retraction is present. Still shows a thrombocytopenia and slightly positive capillary resistance test. Petechiæ disappearing from legs. No hemorrhages since February 9, 1923.

February 17. Discharged well.

Blood changes following splenectomy. (See Table IV.)

1. Hemoglobin and Red blood Cells: The transfusion of 500 cc before the splenectomy raised the hemoglobin to 48 per cent and the transfusion given immediately after the operation produced a further rise to 60 per cent for the hemoglobin and 3,232,000 for the red blood cells. These gradually dropped during the first four days to 38 per cent hemoglobin and 2,832,000 red blood cells. Improvement then set in and at the last examination (May 26, 1923) the hemoglobin was 83 per cent and the red blood cells were 5,120,000. Normoblasts and Howell-Jolly red cells were occasionally present.

* Day following transfusion of 500 cc whole blood.

TABLE IV.—CASE II.—BLOOD EXAMINATIONS AFTER SPLENECTOMY

	Hemoglobin. Per cent.	Red blood cells.	White blood cells.	Platelets.	Polynuclears neutrophiles. Per cent.	Lymphocytes. Per cent.	Monocytes. Per cent.	Coagulation time.	Bleeding time.	Capillary resistance test.	Clot retraction.
After 2 hours*	64	3,232,000	36,000	31,200	93.6	2.6	3.3	....	3 min.		
Dec. 31, 1922	51	2,888,000	55,000	12,000	94.0	1.3	4.3				
Jan. 1, 1923	46	2,992,000	30,400	10,000	90.0	3.0	7.0	....	5 min.		
2, 1923	40	2,896,000	19,400	1,000	89.0	4.0	6.6	....	10 min.		
3, 1923	38	2,832,000	14,000	2,000	82.0	7.3	9.0	....	10 min.		
4, 1923	40	2,656,000	14,400	4,800	80.3	7.0	10.3	....	5 min.		
5, 1923	47	2,884,000	27,000	8,000	74.3	10.3	13.3	10 min.	4 min.	Slightly positive	None.
6, 1923	46	2,936,000	14,000	4,000	75.3	14.0	7.0	....	8 min.		
8, 1923	49	3,450,000	12,000	4,000	72.0	15.6	8.3	....	10 min.		
10, 1923	60	3,992,000	13,200	10,000	73.6	14.3	9.6	7 min.	8 min.	Slightly positive	None.
13, 1923	56	3,520,000	14,400	4,000	75.3	15.3	6.3				
19, 1923	60	4,800,000	21,000	14,000	72.0	18.0	8.0	....	10 min.	Slightly positive	
27, 1923	58	4,536,000	14,400	14,000	59.3	27.0	11.0	11 min.	8 min.	Slightly positive	None.
31, 1923	59	4,480,000	12,000	10,000	53.3	40.3	6.3				
Feb. 3, 1923	76	4,808,000	18,000	6,000	57.3	28.6	11.0	....	4 min.		
7, 1923	76	4,816,000	14,600	8,000	57.0	32.3	8.0	12 min.	3 min.	Slightly positive	None.
14, 1923	80	4,704,000	15,000	12,000	58.6	34.6	4.3	6 min.	3 min.	Slightly positive	Present but slight.
Mar. 23, 1923	80	4,736,000	18,200	14,000	49.6	44.6	4.3	8 min.	3 min.	Negative	Present.
Apr. 6, 1923	81	4,840,000	10,400	20,000	48.0	42.3	9.0	12 min.	2 min.	Negative	Present.
May 26, 1923	83	5,120,000	9,000	50,000	44.3	41.3	10.6	8 min.	2 min.	Negative	Present.

* Done after a blood transfusion.

2. White Blood Cells: Just before the operation there was a leukocytosis of 22,000; six hours after the operation the leukocytes were 36,000 and on the following day they rose to 55,000. The differential blood picture after the postoperative polynucleosis (Fig. 3) showed a persistent monocytosis. (*i. e.*, increase of the large mononuclears and transitionals.)

3. Blood Platelets: The day following the operation there was a slight rise to 31,200, but then gradually fell to 1000 on the third day after the operation. After this they gradually increased to 10,000 and at present are about 20,000 in number. The morphology remained about the same. The day following the operation a few giant blood platelets present in the smears.

4. Bleeding Time: For a month and a half this was prolonged usually over a few minutes, and even as long as twelve minutes. At present this has become normal (two to three minutes).

5. Tourniquet Test (Capillary Resistance): This was constantly present until the third month after the operation. It is now constantly negative.

6. Clot Retraction: There was no clot retraction for six weeks after the operation. This appeared on February 14, 1923, and slight clot retraction is still present, although the blood platelets remain low. It is interesting to note that the blood of this patient never showed clot retraction on previous examinations, but all other evidence of the previous condition is absent. The capillary resistance test is now negative and clot retraction is present.

Summary of Case. Case of Chronic Thrombocytopenia (Four years' Duration): Patient was getting worse as time went on, bleeding more frequently and more severely. Splenectomy brought about a turn for the better and the patient has steadily improved since.

The patient was again seen in April, 1923. Had no hemorrhages since he left the hospital. Gained weight and strength steadily. Static purpura of legs does not occur. The examination of the blood still shows a thrombocytopenia (blood platelets 22,000).

Discussion. A study of the blood changes following splenectomy in our cases brings us a step nearer to the solution of the underlying factors in the production of the thrombocytopenic symptom-complex. This tends to show that first the inhibitory action of the spleen on the megakaryocytes of the bone marrow suggested by Frank,[5] or second, the thrombolytic or blood-platelet destructive action of the spleen as suggested by Kaznelson[17] are not explanatory

theories of the pathogenesis of this disease. The first case described by Kaznelson probably belongs to a different subgroup of the thrombocytopenic purpuræ because he found large numbers of blood platelets in the sinuses of the spleen. Examination of our spleens showed neither in smears nor in cut sections any abnormal increase of the blood platelets, but, on the contrary, a marked diminution of the blood platelets was present. While the spleen apparently assumes a thrombolytic function normally, there is very little evidence outside of Kaznelson's and a few other observations to show that in this type of purpura this supposed action of the spleen is increased.

It is remarkable in all these cases that with the removal of the spleen active hemorrhage immediately stops. This sudden cessation of hemorrhage would indicate that the function of the spleen in these cases could not be taken up so quickly by any vicarious action of other members of the hematopoietic or reticuloendothelial systems. It might indicate that when the spleen was removed some agency became active in inducing the capillaries to contract so as to stop all bleeding. Therefore, it tends to show that the normal spleen has some controlling mechanism on capillary activity through the medium of the blood platelets.

From our observation it would appear that the spleen does not functionate in inhibiting the activities of the megakaryocytes in the production of platelets even though the removal of the spleen is followed by their temporary increase in the circulating blood, because the blood platelets very quickly return to their diminished number or even to a lower level. It would appear, however, that the spleen in these cases does exert an influence on two important properties of the blood platelets, namely, the one which produces clot retraction, and, secondly, on the property of the blood platelets to agglutinate to form thrombi. These properties may be restored immediately after the removal of the spleen or by a later steady development.

We believe that the main process is not entirely an inhibitory or a destructive one on the part of the spleen in this disease, but some damaging and to a certain extent a destructive mechanism

exerted by the reticuloendothelial system on the blood platelets. The damaging mechanism possibly resides in the reticuloendothelial system mainly in the spleen, hemolymph nodes, liver, lymph nodes and bone marrow. Splenectomy, while it does not influence the number of blood platelets in the circulation, induces a cessation of capillary hemorrhage. The influence of the reticuloendothelial system in modifying the quality of the platelets varies in intensity from time to time, but it is always present. When an increase in function occurs it gives rise to the severer types of this disease, or when diminished a milder action is manifest, as indicated when hemorrhage follows ordinary trauma.

Blood platelets have certain important vital properties:

1. They furnish cytozyme (Bordet[27]) for the formation of the blood-clot. Any alteration of this property leads to the condition of hemophilia where the coagulation of the blood is markedly prolonged on account of the delay in the proper formation of cytozyme —the initial step in the coagulation of the blood. In essential thrombocytopenia, cytozyme is rapidly formed, but the amount is necessarily diminished on account of the fewer platelets and the clear citrated purpuric plasma does not clot after standing several hours on account of the sedimentation of the platelets.

2. The blood platelets have an agglutinative property (Bizzozero[28]) by virtue of which they rapidly adhere to cut or injured surfaces of the tissues, resulting in the formation of a thrombus. The minimum number of blood platelets necessary for this action on cut-skin capillaries is very low compared to what occurs in the essential thrombocytopenic state. (See Table III.) In pernicious anemia, leukemia, in a few cases of anemia, we have found platelet counts below 10,000 without any prolongation of the bleeding time. In some cases of essential thrombopenia the bleeding time is prolonged, although the blood platelets may be as high as 250,000. In the rare condition of thrombasthenia the bleeding time is greatly prolonged, although the blood platelets are always over 100,000.

3. Clot retraction is also an important indicator of the condition of the platelets. Clot retraction may appear with less than 20,000 blood platelets. In essential thrombocytopenia this phenomenon

is usually absent, although the platelets may be over 50,000 and in thrombasthenia it is absent with even a greater number of platelets.

This peculiar damaging action on the blood platelets by some element in the spleen and other organs does not account for the diminished number of blood platelets in the circulating blood. Following the initial rise after splenectomy they fall to their low figures, so that we must assume that there is some fault in their formation. The megakaryocytes are not diminished in number in the bone marrow in essential thrombocytopenia but the fragmentation of the pseudopodia of these large cells (Figs. I, II and III) does not take place properly, because the blood platelets in this disease are very large and irregular. Normally, a certain number of blood platelets are destroyed daily in the spleen. The results of such a destructive action in a case with defective blood-platelet formation possibly leads to a further diminution of their number and to an altered function of these bodies.

In some of the operated thrombocytopenic cases the hemorrhagic tendency returned, but not as severe as formerly. Here we must assume that the remaining reticuloendothelial system has taken up the function of the spleen and has exerted its dangerous influence on the few blood platelets formed. To combat this we must turn our attention to some methods of inhibiting the activity of this system. At present we are using *x*-ray therapy and also foreign protein injections (milk, Gram[30]) with encouraging results in some unoperated cases. Their use in splenectomized cases may prove beneficial if in the future a recurrence should manifest itself.

The removal of the spleen is followed by a gradual return of the agglutinative and retractive properties of the blood platelets, although its removal has no effect on their formation. Upon the integrity of the blood platelets depends also the proper tonus and contractility of the capillaries. We need not go into question of the relation of vascular constriction to the number of the blood platelets. O'Connor,[12] Janeway,[13] Hirose[29] and others have shown this intimate relation. It is noteworthy that the capillary resistance tests in our cases were positive for a long time and was slightly positive occasionally in Case I. Since April 24, 1923, it is persistently negative in her case.

CONCLUSIONS. 1. Splenectomy has a definite curative influence on the hemorrhagic factor of chronic thrombocytopenia.

2. It does not seem to be a determining factor in restoring the normal number of blood platelets to the circulating blood.

3. The disease seems to be associated with a disturbed function of the capillary wall in addition to a disordered state of the blood platelets, or it is a result of the diminution of the latter. This is evidenced by the occurrences of purpuric hemorrhages in the skin of the legs on prolonged standing and by the presence of a positive capillary resistance test. With the removal of the spleen capillary resistance test disappears, as does the static purpura.

4. After splenectomy the quality of the blood platelets is restored, as is demonstrated by the reappearance of clot retraction and diminution of the bleeding time to normal.

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DISCUSSION

Dr. H. Z. Giffin, Rochester, Minn.: It is unnecessary to say that this contribution is a very important one, both from the practical and the theoretical standpoints, and Drs. Brill and Rosenthal deserve our commendation for introducing the procedure into this country.

We submitted a case of severe hemorrhagic purpura to splenectomy in the early part of March of this year. The patient had had petechiæ and epistaxis for about one and a half years; metrorrhagia had been present for six months; and in January, 1923, uterine bleeding continued for thirty successive days, the erythrocytes declining to 1,600,000 and the hemoglobin to 18 per cent. It was necessary to give twelve transfusions to maintain the patient's condition. The coagulation time was normal, the bleeding time was prolonged, the prothrombin time was prolonged and the platelet count ranged from 40,000 to 80,000 most of the time. By March 1 the anemia had improved so that the erythrocyte count was over 3,000,000 and the hemoglobin 56 per cent. Splenectomy was then decided upon and it was followed by the same spectacular result which Dr. Brill has described. Six hours after operation the platelet count had risen to 200,000 and the bleeding time had become reduced to two and a half minutes. Four weeks after operation the erythrocyte count was 4,000,000 and the hemoglobin 68 per cent. Contrary, however, to Dr. Brill's observation the platelet count in this case has remained high and the patient has had no bleeding whatsoever since splenectomy. The pathological study of the spleen was interesting and showed an acute splenitis with great numbers of polymorphonuclear cells in the tissue. The results following splenectomy for hemorrhagic purpura opens up a new field of study in connection with the spleen—that of the effect of the spleen on coagulation.

Dr. George R. Minot, Boston: Two years ago I observed a woman who had had this disease at least ten years. During this time petechiæ had been constantly present and small hemorrhages from mucous membranes frequently occurred. The spleen was removed shortly after she was seen. Before its removal the blood platelets were about 10,000 per cu. mm. It was not possible to obtain a count immediately after operation, but forty-eight hours afterward the platelets were about 300,000 per cu. mm. The patient is living and well today, with a normal hemoglobin and the platelets about 155,000 per cu. mm. I think chronic purpura hemorrhagica may be congenital as well as acquired. Some acute cases recover spontaneously, but those of the chronic types rarely, if ever, do so. The pathology of the spleen of the splenectomized case resembles that described by Dr. Giffin.

Dr. E. B. Krumbhaar, Philadelphia: It has been known for some years that a very remarkable increase in platelets may follow removal of the spleen, but it is also known that such a rise is temporary. In regard to this remarkable and really important series contributed by Dr. Brill, I do not think we should feel that because the subsequent fall was not attended by a relapse the platelets have nothing to do with the disease, and I think that Dr. Brill would agree that they are at least connected with the causation of the purpura. I would like to ask, in the 4 cases that were not cured immediately, how do the platelet curves compare subsequently with those of the cases that were cured? Also, was there any relation between the platelet count and the symptoms? It is possible to conceive that, just as in some cases of auricular fibrillation the condition has been permanently relieved by a single interruption of the circus movement with quinidin, so if the platelet rise becomes enough to relieve the condition for the moment, that may be all that is necessary in some cases to prevent recurrence.

Dr. Brill (closing): It was far from my intention to convey the impression which Dr. Krumbhaar obtained that the blood platelets have nothing to do with the pathogenesis of the bleeding in thrombocytopenia. On the contrary, I believe that their function is most important. What I meant to say was that bleeding in this disease did not depend upon the number of blood platelets present at the time in the blood: that it was not justifiable to assume because of the diminution of blood platelets in this disease that hemorrhages occur. This inference is controverted by the facts in our two splenectomized patients, in each of whom blood platelets were far below the number assumed to be necessary (60,000 per cu. mm.) to prevent bleeding—namely, 6000 per cu. mm. in the girl and 20,000 in the boy. In neither of these patients, though the blood platelets have been much below the normal in number, has bleeding occurred since the spleen was removed. What I meant to convey was that bleeding was determined, not by the number of thrombocytes present in the blood, but by their quality. In this respect the size of the platelets after splenectomy is very suggestive, because the most of them are three times or more the normal size of the platelets. Had there been time and the lantern available it was my intention to have Dr. Rosenthal show on the screen slides made from the blood of these patients which revealed larger-sized blood platelets and a few bodies which had all the character of broken parts of megakaryocytes. I believe that blood platelets in the blood whose quality is effective need not be very numerous to prevent the escape of blood from the capillaries, and that bleeding depends perhaps more on the quality than on the number of blood platelets.

I wish to say but one word as to the examination of the spleens in these

2 cases from the view of pathological findings. In both the spleen was enlarged. In the one case the spleen weighed 1400 grams (the girl) and in the other 300 grams (the boy). In both there was an increase in the size of the follicles. There was no change in the endothelial or reticular cells, no increase in reticular fibers, neither the sinuses nor the open spaces contained platelets such as Kaznelson says existed in very large numbers in the spleens examined by him; there was no suspicion of an increase in the reticular fibers. There was a myeloid metaplasia which was the only abnormality found histologically.

Finally, I wish to say that splenectomy furnished a true life-saving measure in cases of thrombocytopenia and seems to cure the disease, though time alone can determine whether the cure is permanent.

EFFECTS OF OPERATIVE INTERFERENCE WITH THE ENDOCRINES ON THE GROWTH AND MALIGNANCY OF A TRANSPLANTED TUMOR OF THE RABBIT[1]

By LOUISE PEARCE, M.D.
AND
C. M. VAN ALLEN, M.D.
(By Invitation)

Introduction. The idea of a relationship between the occurrence and growth of tumors and the endocrine glands has been suggested by both clinical and laboratory evidence, but there is considerable divergence of opinion regarding the part played by the endocrines in these processes. There are observations that removal of the ovaries has a beneficial effect in patients with inoperable mammary carcinoma[1] and partial thyroidectomy has been reported as inducing temporary improvement in inoperable epitheliomas of the tongue and pharynx,[2] while the administration of certain gland products, notably of the thyroid and thymus, to patients with inoperable malignant disease has been advocated by some. That pregnancy has an influence on the occurrence and growth of tumors has frequently been noted clinically, and Slye[3] reports a striking retardation of spontaneous tumor growths of mice as a result of repeated pregnancies. Castration and spaying are also said to exert favorable and unfavorable effects upon certain tumor growths. Among the experimental attempts to investigate the connection of the endocrine glands is the work of Rohdenburg, Bullock and Johnson[4] on the effect of operative removal of various glands of the rat upon the growth of transplanted tumors and the immunity of tumor animals.

[1] From the Laboratories of the Rockefeller Institute for Medical Research.

It was found that these procedures had little effect upon malignancy, although there appeared to be a slight effect on rate of growth and spontaneous recovery.

Attempts to explain such observations are usually based upon the assumption of specific hormone action, but here again conflicting opinions have been expressed, and at the present time it would seem that the entire question is an unsettled one. Experimental investigation in this field has heretofore been limited on account of the material available. Most of the work has been done with the transplantable tumors of the smaller laboratory animals (mouse or rat), in which few metastases are described and in which symptomatic effects are ill defined. Some of these difficulties have now been met by the transplantable epithelial tumor of the rabbit, with which the present study has been carried out.

A detailed description of this tumor and the clinical and pathological history of the animal in which it occurred, together with a number of special phases of its subsequent history, have recently been published[5,6,7,8,9]. Suffice it to say here that the tumor arose in the scrotal skin of a rabbit infected four years previously with Tr. pallidum; the animal eventually showed marked constitutional symptoms and finally succumbed with a widespread distribution of metastatic growths. Successful transplantation from the original animal and for successive generations was made possible by the use of intratesticular inoculations.[7]

The effect of tumor inoculation upon the animal organism varies widely. During the first weeks after inoculation, while the primary testicular tumor is growing, the physical condition of the animal is excellent and usually continues so if regression and eventual healing of the primary tumor occurs with the non-development of metastases. On the other hand, progressive growth of the primary tumor and its extensions, together with the growth of numerous metastases, may eventually be accompanied by a well-marked deterioration in the appearance and well-being of the rabbit. Loss of appetite, loss of weight, emaciation, weakness and roughness of the coat is the usual picture presented by these animals. Between these wide extremes allgrades and degrees of tumor growth are found. From an analysis of the rabbits comprising the first twenty generations of the tumor,

it was found that the average incidence of metastases was 60 per cent and that the distribution of metastases in the average animal was 9.8 per cent of the theoretical possible foci as indicated by the actual location of metastases in the entire group of animals. The mortality in any one series has varied from 0 to 100 per cent, with an average of 20 to 40 per cent,[7] and death generally occurs from six to eight weeks after inoculation.

The clinical and pathological study of rabbits inoculated with this tumor has again forcibly impressed us with the importance of the factor of animal resistance in the processes of disease. Our study of experimental syphilis of the rabbit had led us to the same opinion, namely, that in the course and eventual outcome of the disease the etiological agent is a factor of minor importance as compared with the forces within the animal organism. The striking variations in the disease picture exhibited by different animals in the same tumor series have thus been interpreted upon the basis of variations in animal resistance. The nature or source of the factor of animal resistance seemed to be one of animal constitution which in some way was associated with the endocrine mechanism.[10]

Early in our study of tumor-inoculated rabbits it was found that decided alterations occurred in a number of the organs of internal secretion and in the lymphoid tissue. From the knowledge of the biology of syphilitic infections and from what is known of the influence of this system of organs on animal economy, it was felt that the changes in the glands were not consequences of the disease but possessed a functional significance. In order to investigate this point further, a detailed gross and histological study was undertaken of the thyroid, the parathyroid, the thymus, the suprarenals, the hypophysis and the pineal of all animals inoculated with this tumor. This study has included determinations of weight per unit of body weight. The animals thus studied included a number that died as a result of tumor growth and others that were killed at intervals of from two days to thirty-three weeks after inoculations. As a means of control, similar observations were made upon normal rabbits derived from the same stocks and kept under the same conditions as the tumor animals. The sacrificing of these animals was so arranged as to provide control observations on the condition of these

glands existing at the time inoculation was carried out as well as at the time of determining the effect of inoculation. As a further control, examinations have been made on a large series of animals with various forms of spontaneous diseases and of animals inoculated with Tr. pallidum.[11]

The results obtained from this study of the endocrine glands of tumor inoculated rabbits have been analyzed with reference to the growth and malignancy of the tumor as indicated by the clinical course of the disease, including the growth of the primary tumor and conditions existing at the time of death. It was found that the growth of the tumor was definitely associated with marked alterations in the size and general appearance of the thyroid, the thymus and the suprarenals, and that less pronounced changes occurred in the parathyroids and hypophysis. Distinct histological changes also occurred in the thyroid, the thymus and the hypophysis.

Upon the basis of the evidence thus accumulated the conclusion was reached that the dominant influence in determining the course of the disease was the constitutional organization of the animal, and that from this standpoint the endocrine glands occupied a position of the foremost importance in the mechanism of animal resistance. In order to determine which glands were responsible and the extent to which the course of the disease could be influenced through this mechanism, several different lines of investigations were carried out, including the use of chemical agents and the effect of operative interference. The experiments here reported deal with the results on tumor growth of operative interference with the thyroid, thymus and suprarenals. As a means of control, similar surgical procedures were carried out without interference with the endocrine glands and parenchymatous organs; an additional group was composed of splenectomized rabbits. Each series also included at least 5 normal unoperated controls.

Carefully selected adult male rabbits from one to two years of age, or slightly younger animals approaching maturity, were used. They were separately caged and were kept under the same conditions of shelter and feeding. Inoculations of 0.2 cc of a salt solution emulsion of tumor tissue were made into one testicle. The animals were examined almost daily and clinical notes made on the state

of the primary tumor, the occurrence and growth of clinical metastases and the physical condition of the animals. In addition, careful measurements of the primary tumor were made three times a week and the animals were weighed twice a week. The duration of the experiments was fixed by previous observations of the time at which death or recovery was most likely to occur from tumor growth. In order to cover the critical period the experiments were allowed to run seven to eight weeks after inoculation and then terminated by killing, with ether anesthesia, all surviving animals. Complete postmortem examinations were made, including the weight of the endocrine glands and other organs, and the distribution, amount and character of tumor tissue present in each animal were carefully noted. Thus it was possible to correlate the clinical course of the disease and the condition at the time of death with the postmortem findings.

Up to the present time the following experiments have been carried out:

Series 1.	Nov. 10, 1922.	7 complete thyroidectomies, 5 partial thyroidectomies and 7 normal controls.
Series 2.	Nov. 23, 1922.	5 complete thymectomies and 6 normal controls.
Series 3.	Dec. 13, 1922.	6 complete thyroidectomies; 7 animals in which operative procedures on the suprarenals had been performed; 6 splenectomies; 9 operated controls and 5 normal controls.*
Series 4.	Mar. 1, 1923.	6 complete thyroidectomies, 6 partial thyroidectomies, 7 thymectomies and 6 normal controls.

Effects of Operations on the Thyroid. On account of the apparent importance of the thyroid and the ease with which operations on this gland are performed, the majority of our experiments on the effect of disturbance of the endocrine function have been

* In the present summary this series is selected as a basis for a description of the results obtained.

concerned with a study of the effects of various degrees of surgical interference with thyroid function. Two types of procedure have been employed: First, the complete removal of the thyroid, and second, partial removal or partial removal plus ligation of the blood-vessels to the remaining lobe.

It was found in each experiment that complete removal of the thyroid gland before inoculation (three to seventeen days) or subsequent to inoculation (7 days) produced a marked lowering of the resistance of the animal. This alteration in resistance was expressed first in an increased rate and extent of the primary growth as shown in Chart I, which records the calculated volume of the primary

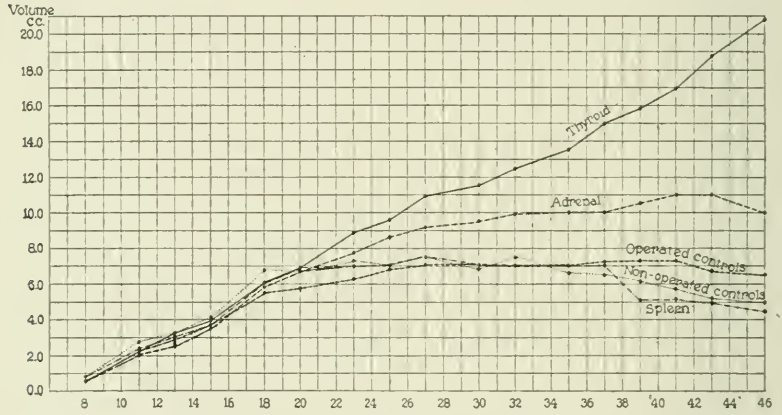

CHART I.—Effect of operative interference with the endocrines on the primary tumor growth.

tumor growths of various groups of animals in one experiment. By the end of the third week the primary tumors of the six thyroidectomized animals were distinctly larger than those of the other groups, and this disproportion increased and continued to the end of the experiment. In this particular series the operation was performed one week after inoculation, so that the beginning of greater growth of the primary tumor in these animals was initiated two weeks after removal of the thyroid. In another series in which the operation was carried out before inoculation, differences in the extent and degree of the primary testicular tumor were observed within ten days. The greater extent of primary growth in the completely

thyroidectomized animals is also shown by the constant occurrence of tumor involvement of the head of the epididymis and the spermatic cord. While such extensions are not uncommon in normal rabbits or under various experimental conditions, the frequency and degree with which they occur in the completely thyroidectomized animals is indicative of the inability of the host to limit the primary growth to the confines of the testicle and tunics.

The lowering of resistance brought about by complete thyroidectomy is likewise shown by the absence of any tendency or a greatly lessened tendency toward regressive changes on the part of the primary tumor. An indication of this condition is seen in Chart I, in that the line representing the size of the primary tumor in the group of thyroidectomized animals maintains an increasing upward

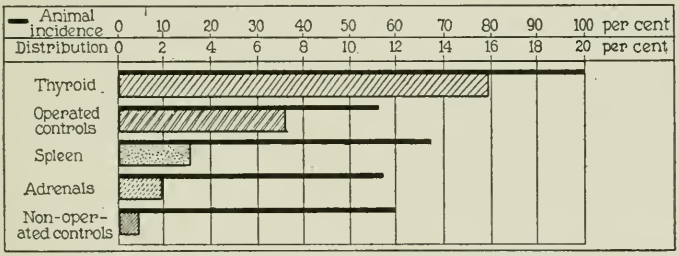
Animal incidence
0 10 20 30 40 50 60 70 80 90 100 per cent
Distribution
0 2 4 6 8 10 12 14 16 18 20 per cent
Thyroid
Operated controls
Spleen
Adrenals
Non-operated controls

CHART II.—Effect of operative interference with the endocrines on incidence and distribution of metastases.

trend. There is no suggestion of either a decrease in size or of the maintenance of a more or less stationary level. Postmortem examinations of the primary tumor and its epididymis and cord extensions in these animals revealed a large amount of viable tumor tissue—in some instances there was only a slender central core of necrotic material. Moreover, the encapsulation of these tumors was slight, the surrounding fibrous tissue being extremely thin and delicate.

A further expression of the decreased resistance of the thyroidectomized animals is the practically constant development of metastases with a more rapid progress of the disease as a whole. The metastases found clinically have always been more numerous and have been detected earlier than in other operated conditions or in normal animals. In the experiment illustrated by Charts I and II

the animal incidence of metastases in the thyroidectomized group found at autopsy was 100 per cent while the incidence of the four other groups averaged 60 per cent, which corresponds to the average animal incidence of the first 20 generations of tumor transplants. The greater distribution of metastases in this group is also striking—16 per cent. It is more than twice as great as that of the next largest group—the operated controls. The results in the other experiments were similar, that is, both the incidence and distribution of metastases in the completely thyroidectomized animals exceeded that of the normal controls. Finally, the lessened resistance of thyroidectomized rabbits to tumor growth is strikingly brought out by the higher mortality rate and the greater frequency of the acute fulminating type of disease. Of the 6 animals whose thyroids had been completely removed, 4 (67 per cent) died or would have died within a few hours of the time they were sacrificed. In the two other experiments the mortality figures for these groups were 57 and 67 per cents as contrasted with the control values of 14 and 50 per cents.

The influence of a partial thyroidectomy upon tumor growth is not as constant as that of a complete removal of the gland. In our first series of 5 animals (November 10, 1922) removal of one lobe and the isthmus with the ligation of the blood supply of the remaining lobe produced a marked increase in the resistance of the animal to the growth of the tumor as compared with the normal controls. The rate of growth of the primary tumor was slower than that of the normal animals and the tumors remained smaller and firmer with a greater degree of encapsulation. There was a greatly lessened tendency to metastasize and no evidence of constitutional disease. In one animal, one metastasis was detected clinically late in the course of the experiment and at autopsy a fair number of metastases were found. In only one other animal were there any secondary growths, and these consisted of two small extensions from the primary tumor. Considered upon a percentage basis the figures for this group are: Animal incidence of metastases, 40 per cent; distribution of metastases, 1.5 per cent. The disease in the normal controls, on the other hand, was more extensive both as regards the primary tumor and the occurrence and type of metastases. Thus in 7 normals the animal incidence of metastases was 80 per cent with

a distribution of 11 per cent. Moreover, the mortality rate was zero while that of the control animals was 14 per cent.

It is not certain, however, that an effect of this kind will follow partial thyroidectomy in all cases. In another series of animals (March 1, 1923) the growth of the primary tumor was more active than in the animals with the thyroid completely removed. However, in an analysis of the postmortem findings the distribution of metastases was somewhat less than in the normal animals and considerably less than in the thyroidectomized group, while the proportion of living tumor tissue in the partially thyroidectomized animals was less than in those rabbits in which the thyroid had been completely removed or in the normals. In addition the mortality rate of the partial thyroidectomy group (33 per cent) was lower than that of the control animals (50 per cent.) While partial removal of the thyroid apparently produces an augmentation of the animal's resistance to tumor growth, it is evident that the degree of this effect is variable. There are many factors which might conceivably influence or modify the effect of this type of operation, but there are at least two which must be considered in evaluating the results of the second experiment as contrasted with those of the first. The tumor was definitely more malignant than it was at the time of our first experiment, and the interval of time between operation and inoculation was considerably shorter in the second series.

Effect of Operations upon the Thymus. Thus far only one type of operation has been undertaken, that of complete thymectomy. Tumors in thymectomized animals grow comparatively slowly, and during the first few weeks the rate of growth is even less than that of normal animals. The primary tumors appear in most instances as rather small, indurated nodules, but growth is continuous and eventually the tumor reaches a size greater than that of control animals. In the first experiment metastases occurred in 4 of the 5 thymectomized animals, but in most instances were slow in appearance and development; the incidence of metastases in the controls was the same, but the distribution was less extensive. The mortality rate of the thymectomized and control animals was 20 and 17 per cent—one animal in each group died at the same time and with a comparable amount and distribution of metastases.

The thymus in the control animal had been practically replaced by tumor tissue, so that in reality this animal represented one in a thymectomized state. Such a picture is not infrequently seen, and it is of interest that in animals showing extensive metastatic involvement of the thymus metastases to the bones are unusually frequent. In a second experiment carried out when the tumor was much more malignant the final disease picture in the thymectomized animals was less severe than in the controls. The character of the primary growth, however, was similar to that observed in the first experiment.

Our present interpretation of the effect of thymectomy is that under certain conditions the resistance of the animal to tumor growth is distinctly decreased, but not to the same degree or probably in the same way as with complete thyroidectomy. The entire disease progresses at a slower rate than in the completely thyroidectomized animals, and the outstanding feature is that the picture presented reminds one in many respects of that seen in old animals.

Effect of Operations upon the Suprarenals. Since it appeared doubtful that the removal of one gland would produce any serious immediate or delayed alteration in the functional capacity of the suprarenal mechanism, it was decided to destroy as much of the cortex of both glands as possible. This was accomplished with the thermocautery at one operation and the attempt was made to destroy at least three-fourths of each gland.

In several instances the primary tumor showed a comparatively rapid initial growth followed by almost complete suppression occurring within a few weeks after inoculation. The other animals of the series showed a slow initial but a more continued growth, with the development of large primary tumors which ultimately regressed slightly. There were 7 animals in the group and in 4 of them (58 per cent) there were metastases. This incidence is comparable with the normal controls, although the distribution is slightly greater (Charts I and II). The mortality rate in both the suprarenal operated animals and the normal control groups was the same—zero. In many respects the results obtained in this experiment were comparable to those of the normal controls, but there were significant differences. Among the more important of these was the character

of the primary tumor. Clinically the majority of the tumors were unusually large, as may be seen in Chart I, although they do not approach the size of the primary growth of the completely thyroidectomized rabbits. In addition extensions to the epididymis and cord were much less frequent and were considerably smaller and more thickly encapsulated. In most of the animals of this group a comparatively slight decrease in size of the primary tumor occurred toward the end of the experiment despite the fact that by palpation one could detect obvious signs of regression. Absorption of necrotic tissue was relatively slight, and at autopsy the primary growth was extremely heavily encapsulated. There was but one instance in which a renewal of growth of the primary tumor occurred during the last week of the experiment, and postmortem examination revealed the presence of a small but active, non-encapsulated, metastatic nodule of the liver as well as active metastases in both suprarenal glands. There is probably no doubt that had this particular animal been allowed to live the disease would have ultimately assumed a malignant character.

When one compares this group of rabbits with the other operated groups, one is at once impressed with the increased resistance displayed as regards both the incidence and distribution of metastases and the lower mortality rate. One must consider the part played by the operation itself, but apparently the major factor is the damage done to the suprarenals themselves, either as a result of changed activity or a disturbance of relationships existing between the suprarenals and other glands. A comparison between this group of 7 animals and the 5 normal non-operated controls shows a well-marked difference in the actual size of the primary tumor, which is all the more striking when one considers the relatively large amount of non-absorbed necrotic tissue in the suprarenal animals. On the other hand, there is comparatively little difference as regards the incidence and distribution of metastases. The number of animals in each group is too small to admit of final conclusions, but the effect of extensive injury to the suprarenals is all the more striking in view of the fact that the disease in the normal controls of this particular experiment was less severe than has been the case in normal animals during the past winter. A comparison with the

operated control group, which includes 3 animals in which a similar abdominal operation had been performed, emphasizes again that injury to the suprarenals had apparently increased the factor of animal resistance, with the result that the disease was extremely mild (Charts I and II). In addition the results obtained after complete thyroidectomy are in sharp contrast to those following suprarenal injury, so that, considered from the point of view of animal resistance, we would interpret the effects of our surgical procedures in this experiment as operating to decrease animal resistance in the one case and to increase it in the other.

Controls. *Normal Animals.* The growth of the primary tumor and the course of the disease in normal rabbits are subject to rather wide variations both as regards the individual animals in any one series and as regards different series as described in previous papers already referred to. In general terms, however, it may be stated that of a group of 5 animals, in one the disease pursues a highly malignant course (decreased resistance); in another, the disease is mild and ultimately recovery occurs (increased resistance), while in the remaining 3 animals the course and outcome of the disease varies between these two extremes. An analysis of the postmortem examinations of the first twenty generations of tumor growth has shown that the animal incidence of metastases was 60 per cent, while the average distribution of secondary growths was 9.8 per cent. The ultimate mortality in any particular series has varied from 0 to 100 per cent, with an average of 20 to 40 per cent.

Viewed from this standpoint the disease in the normal controls in the experiment illustrated by the accompanying curves is seen to have been less severe than the average. The growth of the primary tumor was rapid and extensive, as shown in Chart I, and in 4 of the 5 animals there was a moderate to marked involvement of the head of the epididymis, and in 1 there was a moderate cord extension. The further progress of the disease, however, was unusually mild. The primary tumor in 2 of the 5 animals was healed at the conclusion of the experiment and in the others it was largely necrotic and surrounded by a moderately thick fibrous capsule. Early clinical metastases were found in 1 animal and at autopsy metastases were present in 3 of the 5 animals (60 per cent), but they were compara-

tively few in number with a limited organ distribution (1 per cent). None of the normal controls died. The disease of the normal controls in other operated series has varied from a similar mild condition to extremely malignant limits in which the animal incidence of metastases was 83 per cent with an organ distribution of 18.8 per cent and a mortality rate of 50 per cent. The variations in the disease picture in the normal ani nals of each experiment have been used as a basis upon which to evaluate the effects produced by any operative procedure employed in that series. Finally, all the experiments have been assembled and the results of each compared with the others.

Controls. *Operated Animals.* Three types of operative procedures were employed as control measures to operations upon the endocrine glands. These consisted in duplicating the entire surgical procedures employed in thyroidectomy, thymectomy and cauterization of the suprarenals except that the endocrine glands and parenchymatous organs were not interfered with in any way In the case of the abdominal control operations a small area of retroperitoneal fat in both upper flanks was cauterized. In the experiments illustrated by the accompanying charts there were 3 animals in each group: cervical, thoracic and abdominal.

The effect of these operative procedures appeared at first to increase the resistance of the animal to tumor growth in that there was some evidence of restraint upon the growth of the primary tumor during its earlier stages. Following this period, the growth of the primary tumor paralleled that of the normal controls. Toward the end of the experiment, however, 2 of the 9 animals continued to show a well-marked primary growth, and hence the curve in Chart I, representing the size of the primary tumor, shows only a slight decline from the previous level. At the conclusion of the experiment the primary tumor was healed in 3, largely necrotic in 4 and partly necrotic in 2 rabbits. Extension of the testicular tumor to the head of the epididymis and spermatic cord occurred in 8 of the 9 animals as contrasted with 4 of the 5 non-operated controls, and the degree of these extensions did not exceed that in the normal animals.

The animal incidence of metastases in the operated control group was 57 per cent (Chart II), but with the exception of the completely

thyroidectomized animals there is no striking difference between this figure and that of the other groups in the experiment, and it is comparable with the average figure of 60 per cent of the first 20 generations of the tumor. The distribution of metastases, however, 7 per cent, was considerably greater than in the other groups except the thyroidectomized animals, though less than the average figure of 9.8 per cent. In 2 of the 9 animals the disease was fairly malignant, in 4 it was mild and in the remaining 3 rabbits its character may be described as midway between these extremes. While the mortality rate of the operated control groups (22 per cent) is considerably above that of the normal controls of this experiment, it is still well within the limits of the average rate of our general experience (20 to 40 per cent). It would appear, therefore, that the course of the disease cannot be said to have been materially affected by operative procedures *per se*. Animal resistance was not impaired to the extent or degree brought about by thyroidectomy nor was it increased to the level apparently induced by injury to the suprarenals.

Splenectomy. For a further surgical control as well as the possible bearing such a procedure might have on the endocrine mechanism, the spleen was removed from 6 rabbits prior to tumor inoculation.

The results obtained from this operative procedure are not indicative of any definite effect upon the mechanism of animal resistance. Taking the group as a whole, the growth of the primary tumor was similar to that of the normal animals, although slightly less in degree, as seen in Chart I. Of the 6 animals comprising the group, 1 developed a malignant condition both as regards the primary growth and the occurrence of metastatic tumors, and was killed, thus giving a mortality rate of 17 per cent for the group. At the conclusion of the experiment the primary tumor was healed in 2 animals and there were no metastases; in 2 rabbits the primary tumor was entirely necrotic and in the last animal of the group it was partially so, while the metastatic growths were few in number. Such a distribution of variations in the clinical course of the disease usually occurs in normal animals, although in this particular experiment the actual distribution of metastases was somewhat greater than in the controls (Chart II). On the whole, however, the percentage distribution of

different types of tumor growth was within the range of normal variation, and we are inclined to interpret the results as representing mainly the effect of an abdominal operation plus individual peculiarities on the part of different animals.

Discussion. On the basis of clinical and pathological observations obtained during a study of a transplantable malignant epithelial tumor of the rabbit, the relation of the glands of internal secretion to tumor growth was given detailed consideration. The preliminary results obtained by operative procedures on certain of the endocrine glands are here reported, and are considered from the point of view of animal resistance as shown by the effect produced upon the growth and malignancy of the tumor.

It was found that complete thyroidectomy performed before inoculation or shortly thereafter decreased animal resistance to such a degree that the growth of the primary tumor far exceeded that in normal rabbits, and that, in addition, there was little or no tendency toward ultimate regression and absorption. Moreover, the incidence and the distribution of metastatic growths have, in each experiment, been greater than in the control animals or than the average values obtained in a large number of normal animals (twenty generations). An even more striking evidence of lessened resistance to tumor growth induced by complete removal of the thyroid is the increased mortality rate in these groups irrespective of such factors as variations in the malignancy of the tumor. Thus the mortality rate of the thyroidectomized groups has varied from 57 to 67 per cent while that of the normal controls of the experiments has been from 0 to 50 per cent; and it is significant that the average mortality of the thyroidectomized groups (64 per cent) is almost equal to the average animal incidence of metastases of the other operated groups (70 per cent), in which the average death rate is much lower, namely, 17 per cent. In addition the progress of the disease in many of these animals was unusually rapid and death occurred as early as four or five weeks after inoculation. The conclusion has, therefore, been reached that in rabbits deprived of the thyroid gland shortly before or after inoculation the growth and malignancy of the tumor is greatly enhanced.

The effect of partial thyroidectomy is less clear. In one series

the effect of a partial removal of the thyroid gland was markedly to increase animal resistance, as shown by the character of the primary tumor, the incidence and distribution of metastases and the mortality rate. The initial growth of the primary tumor was considerably smaller than that of the controls and regression, encapsulation and healing were early prominent features in these animals. In addition, few metastases were found and all animals survived the period of the experiment, as contrasted with a mortality rate of 14 per cent in the control group. However, the restraining effect of partial thyroidectomy upon tumor growth was not always found to be so marked, as was the case in a second experiment. But judged from the standards of incidence and distribution of tumor and mortality rate the disease of the partial thyroidectomized animal was still less severe than in the normal controls. There are, however, at least two factors relating to this experiment which undoubtedly are concerned in the less pronounced effects induced by the operation. At the time of year at which the second experiment was carried out the tumor was considerably more malignant than it had been during the previous months and the interval of time between operation and inoculation was shorter. It appears, therefore, that the effect of partial thyroidectomy on tumor growth is not entirely constant. The severity of the disease process in these animals seems to rise and fall parallel with but distinctly below that in normal controls. The completely thyroidectomized rabbits, on the other hand, hold to a constant level of malignancy at all times. It would appear, then, that animals retaining a small portion of the thyroid are influenced by the same extraneous factors as are normal rabbits, factors which show little or no effect upon animals deprived of that gland.

The effect of complete removal of the thymus is likewise not entirely clear. The striking feature in these experiments was that thymectomized animals behave in general like old animals. The primary tumors grew much more slowly than in normal rabbits, but eventually became larger and remained so. Clinical metastases were comparatively late in appearance. In one series the disease was distinctly more severe than that of the controls, judging from the growth of the primary tumor and incidence and distribution of

metastases seen at autopsy. The growth of the primary tumor in another experiment was likewise greater than the controls, but the disease, as a whole, was less severe. Here, again, the factors of increased malignancy of the tumor, and perhaps the time interval between operation and tumor inoculation will have to be considered.

From the results of these two experiments it is obvious that only an impression of the effect of thymectomy on tumor growth may be expressed. However, if one also takes into consideration the condition of the thymus in instances of a highly malignant disease[7] it would appear at least probable that the partial or total absence of this gland was intimately concerned with a state of lessened animal resistance.

Extensive injury to both suprarenals (thermocauterization) apparently induces a distinct increase in animal resistance. The initial growth of the primary tumor in some of the animals was unusually rapid and in others it was slow and continuous; but although an extensive necrosis occurred in the majority of instances the usual process of absorption was relatively slight, due in part to the unusually heavy encapsulation of the growth. The figures for the incidence and distribution of metastases are practically the same as those of the normal controls in which the disease was very mild, but they are far below the average figures for normal animals of the first twenty generations. A comparison with the operated controls, moreover, emphasizes the fact that the potential malignancy of the disease was held in check in the suprarenal animals. There were some indications, however, of the failure to maintain a condition of increased resistance to tumor growth late in the course of the experiment. Such a transition of the state of the body's defensive mechanism is open to many interpretations, but the possibility of an exhaustion following a period of high functional activity of the endocrine system, either in whole or in part, is in line with our knowledge of what occurs in the progress of the disease in normal animals.

The growth of the primary tumor and the progress of the disease do not appear to be influenced in any significant respect in rabbits whose spleen has been removed or in those subjected to a number of so-called "non-specific" surgical procedures in which the endocrine glands were not disturbed. Of the 15 rabbits comprising these groups,

3 showed a considerable primary tumor, and at the conclusion of the experiment a widespread distribution of metastatic tumors; in 5 the primary tumor was healed and 1 metastasis only was found; in the remaining 7 rabbits the primary tumor was moderately or largely necrotic and the number of metastases were within the limits of variation found in normal animals. These results correspond to those obtained by inoculations of many series of normal animals, although they are higher than those obtained in the non-operated controls of this experiment. There was no striking difference, however, in the disease picture presented by the operated controls, and, as far as our experiments have gone, the conclusion has been reached that splenectomy and minor and major operative procedures *per se* exert no essential influence upon the growth and malignancy of this tumor.

Complete removal of the thyroid gland has resulted in conditions which permit the growth of the primary tumor and the course of the disease as a whole to progress at a rate and to a degree far beyond that seen in normal animals. Partial removal of the thyroid, on the other hand, tends to operate in the opposite direction, and in animals with an incomplete as contrasted with a complete thyroidectomy the growth of the primary tumor is less pronounced, the incidence and distribution of metastases are less marked and the disease is less severe. Complete removal of the thymus produces an effect somewhat similar to that of complete thyroidectomy, although not to the same extent or degree, and there have been certain significant individual exceptions. Extensive injury to both suprarenal glands has uniformly restrained the malignancy of the disease as seen by the character of the primary growth, and the incidence and distribution of metastases, although there are certain indications that such an effect may not be permanently maintained.

It is at once evident that the character of the result obtained by operative interference upon certain individual endocrine glands is not invariably the same, notably so in the case of partial thyroidectomy and complete thymectomy. It is conceivable that with operations of this type other factors which may affect the course of the disease are permitted to exercise a more potent influence. From the evidence at our disposal a most significant factor is the degree of

malignancy exhibited by the tumor at the time of the experiment. Since the question of malignancy itself is considered as intimately bound up with the endocrine mechanism from the point of view of animal resistance, variations in malignancy may occur as a result of many extraneous forces operating through this mechanism. On the other hand, there is a tendency toward a similarity of effects produced by surgical interference with different endocrine organs. Thus certain operative procedures carried out with the thyroid (partial thyroidectomy) and the suprarenals (extensive thermocauterization) may bring about a state of increased resistance to tumor growth, so that in these animals the disease exhibits a lessened malignancy. Complete thyroidectomy and complete thymectomy may also be followed by a similar though not an identical diminshed resistance to tumor growth, and consequently a disease of greater malignancy.

Finally, we should like to point out that the effects upon tumor growth produced by a variety of agents such as *x*-rays and radium, parenteral injections of foreign proteins, colloidal solutions and so-called inert substances, resemble in many particulars the effects obtained in our experiments by surgical interference with the endocrine mechanism. From a number of experiments with such substances, it appears not unlikely that their influence upon tumor growth is exerted by reason of their effect upon the endocrine mechanism and thus upon the general state of animal resistance.

Conclusions. The experimental evidence so far obtained indicates that the growth and malignancy of a transplantable epithelial tumor of the rabbit may be markedly influenced by surgical interference with certain of the endocrine glands such as the thyroid, the thymus and the suprarenals. Furthermore, it is suggested that the result of such a disturbance of the endocrine mechanism operates through the function of animal resistance and economy.

From this point of view the relative value of individual endocrine organs is of less importance than the integrity and balance of the system as a whole.

Finally, these experiments furnish additional evidence of the significant influence exerted by the endocrine mechanism upon the natural state of animal resistance.

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DISCUSSION

Dr. Henry Sewall, Denver, Colo.: Did you make any combined gland operations, and if so, what was the effect?

Dr. Wade H. Brown (closing): We did not do any combined operations. We employed procedures that were as simple as possible in order to determine effects referable to individual organs. However, we have used chemical agents such as potassium iodide, which affects not only the thyroid but the entire endocrine mechanism—especially the thymus—and substances of this character also influence the growth of the tumor.

A CLINICAL STUDY OF DIGITALIS TOXEMIA

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AND

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Opinions differ greatly as to what proportion of regular hearts are slowed by digitalis administration. Stimulating the vagus nerve by pressure in the cervical region often results in slowing of the whole heart. On the other hand, digitalis is supposedly an ideal cardiac remedy because it increases irritability, tonicity and contractibility while decreasing conductivity. If the irritability of the pacemaker of the heart is increased by digitalis, it would seem that the rate of regular hearts should be increased by it. There is no uniformity of opinion as to the correct amount of digitalis to be given cases with regular hearts and heart failure in order to get maximal improvement of tone. A number of good observers think that only the amount of digitalis which can be eliminated in twenty-four hours—20 minims in a child and 30 minims in an adult—is necessary to give a maximal increase of tonicity. Anything more than that is considered by them to be useless and often dangerous to the patient. A point under discussion also is the relation of nitrogen retention in the blood to digitalis elimination.

We undertook the study of these points in June, 1922, in a group of 50 patients on the Second Medical Service of the New York City Hospital. To the other visiting physician and the house physician on the Second Medical Service we are indebted for their hearty coöperation.

Hatcher had shown that nausea in digitalis administration was due to direct effect of the drug upon the heart itself rather than upon the central nervous system. In order to note the maximal clinical

improvement, it was decided to push these patients to the point of nausea, recording meanwhile the findings.

Daily observations of the amount of digitalis administered, the ventricular rate and rhythm, the blood-pressure, nausea, vomiting, edema, cyanosis, hydrothorax, dyspnea, confused mental state, vertigo, tone of heart sounds and, where practical, the weight was made. Fluid intake and output charts, outside of a metabolism ward with special nurses, were considered too inaccurate to be of much value. Care was taken to see that patients received no other drug during the period of the digitalis tolerance test, and that in the case of up-patients they had been lying down for at least five minutes before having their ventricular rate counted. No constantly febrile cases were treated. Cases with edema were given, in most instances, the benefit of ten days' rest in bed on a salt-poor diet with restricted fluids before the administration of digitalis. Electrocardiograms were not taken.

We expected to continue the test over a considerable period of time and did not care to use preparations of the tincture of digitalis containing different amounts of the absorbable, chloroform-soluble fraction. Dr. Robert A. Hatcher, of the department of pharmacology of Cornell University, was asked to prepare for us a sufficient quantity of a standard tincture to use for all cases to be tested. This he very kindly did. His description of the preparation used is as follows:

"The tincture used in this investigation was prepared with care according to the directions given in the United States Pharmacopœia from an active specimen of powdered digitalis, and, after the activity had been determined by means of the cat test, the activity was adjusted so that 1 cc represented 1 cat unit."

This tincture was used over a period of ten months. At different times throughout its use young fibrillators were tested with it. Their ventricular rates were routinely slowed to 70 contractions per minute by dosage averaging 0.15 cc per pound of body weight. The drug was usually administered in the amount of 4 cc three times a day, after meals, in plain water.

The already well-established opinion that the vehicle used in administration has no bearing upon the development of nausea was confirmed by 1 case. In July, 1922, he received 84 cc of tincture

of digitalis administered in plain water, over a period of seven days, before the development of nausea. Four months later his tolerance was unchanged when peptonized milk was used as a vehicle.

Eggleston,[1] in 1916, found in experimental work on dogs that atropine does not interfere with emesis induced by digitalis.

In 3 cases we failed to relieve vomiting by pushing atropine hypodermically to the point of wide dilatation of pupils and dry mouth.

The nausea point was determined as follows: The number of cubic centimeters of tincture was totaled. The average daily elimination by adults of tincture of digitalis, as shown by the amount necessary to keep properly slowed fibrillators in balance, is 2 cc. Accordingly, 2 cc for each day of digitalis administration was deducted and the result divided by the patient's body weight less edema.

Eggleston and Wyckoff,[2] in a group of 20 patients, found that the average emetic dose of the purified tinctures was 0.113 cat unit per pound of body weight. Our figures in a group of 50 cases are a little more than double that of Eggleston and Wyckoff. The widest individual variation in drug tolerance was noted. The lowest figure noted was 0.12 cc. The highest was 0.55 cc in a man of small frame who took 88 cc in eight days.

Date, March, 1923.	9	10	11	12	13	14	
CC of digitalis	12	12	12	12	0	0	
Ventricular rate	76	100	104	88	90	88	
Ventricular rhythm	R.	R.	R.	R.	R.	R.	
Blood-pressure	130/18	128/90	124/84	140/92	130/90	114/70	
Nausea	N.	N.	N.	Y.	Y.	N.	
Vomiting	N.	N.	N.	Y.	N.	N.	
Edema	N.	N.	N.	N.	N.	N.	
Cyanosis	N.	N.	N.	N.	N.	N.	
Hydrothorax	N.	N.	N.	N.	N.	N.	
Dyspnea	±	±	±	±	±	±	
Confused mental state	N.	N.	N.	N.	N.	N.	
Tone of heart sounds	Fair	Fair	Fair	Fair	Fair	Fair	
Weight	110						
Total quantity of digitalis administered	...	...	...	...	...	...	48 cc.
Over period of days	...	...	...	...	...	...	4
Nausea point	...	...	...	...	...	...	0.33
Days of Nausea	...	...	...	...	...	...	2
Days of vomiting	...	...	...	...	...	...	1

Y = Yes; N = No; A.F. = Auricular Fibrillation; C.B. = Coupled Beats; H.B.P. = Heart Block Partial; H.B.C. = Heart Block Complete; A.Fl. = Auricular Flutter; P.C. = Premature Contractions; R. = Regular; ± = Slight.

[1] Jour. Pharmacol. and Exper. Therap., October, 1916, ix, 11.
[2] Arch. Int. Med., August, 1922, xxx, 2.

The age of the patients seemed to bear little relation to digitalis tolerance. The average age of the group was fifty-four years. Only one patient less than twenty years of age was tested.

Digitalis tolerance test of Michael Fabian, aged sixty-four years. Diagnosis: 1. Arteriosclerosis generalized. 2. Pulmonary emphysema. 3. Old fracture of left thigh.

The cases have been divided into various groups and the results summarized as follows:

REGULAR HEARTS WITHOUT EVIDENCE OF HEART FAILURE, 27 CASES

Digitalis Nausea Point: Averaged 0.26 per pound of body weight.

Effect on Rate: 6 patients showed slowing of the heart totaling 93 points. 6 patients showed increased rate totaling 97 points. 15 patients were unaffected. The group average showed practically no change.

Effect on Blood-pressure: Systolic blood-pressure was decreased on an average of 3 points.

Diastolic blood-pressure was decreased on an average of 6 points.

Development of New Rhythm: 1 case developed premature contractions.

Average Duration of Nausea: 2 days.

Average Duration of Vomiting: 1 day.

Patients Improved by Treatment: None.

Patients Made Worse by Treatment: None.

REGULAR HEARTS WITH EVIDENCE OF HEART FAILURE, 7 CASES

Digitalis Nausea Point averaged 0.28 cc per pound of body weight.

Effect on Rate: 2 patients showed slowing of the heart totaling 46 points. 1 patient showed increased rate totaling 16 points. 4 cases were unaffected. The group showed an average decrease in rate of 4 points.

Effect on Blood-pressure: Systolic blood-pressure was decreased on an average of 3 points. Diastolic blood-pressure was decreased on an average of 6 points.

Development of New Rhythm: None.

Tone of the Heart: Showed moderate improvement in 57 per cent of the cases.

Average Duration of Nausea: 2 days.

Average Duration of Vomiting: 1 day.

Patients Improved by Treatment: Four cases showed moderate improvement.

Patients Made Worse by Treatment: None.

CASES WITH AURICULAR FIBRILLATION, 8 CASES

Digitalis Nausea Point Averaged 0.28 cc per pound of body weight.

Effect on Rate: All cases showed marked reduction in ventricular rate save for two slow fibrillators whose rate was reduced only 8 and 12 points respectively. The average reduction in ventricular rate was 42 points.

Effect on Blood-pressure: Systolic blood-pressure was decreased on an average of 8 points. Diastolic blood-pressure was decreased on an average of 5 points.

Development of New Rhythm: 1 case developed what was apparently a complete heart-block with a regular ventricular rate of 39 per minute. This condition persisted for eleven days, during which the patient was comfortable. The rhythm then returned to that of auricular fibrillation.

Average Duration of Nausea: 2 days.

Average Duration of Vomiting: 1 day.

Patients Improved by Treatment: All cases in the group.

REGULAR HEARTS WITH RENAL DISEASE AND MODERATE NITROGEN RETENTION, 8 CASES

Digitalis Nausea Point averaged 0.29 cc per pound of body weight.

Effect on Rate: 5 cases showed slowing of the heart totaling 95 points. 1 case showed an increased rate of 18 points. 2 cases were unaffected. The group showed an average decrease in rate of 11 points.

Effect on Blood-pressure: Systolic blood-pressure was decreased on an average of 5 points. Diastolic blood-pressure was decreased on an average of 5 points.

Development of New Rhythm: 1 case developed occasional premature contractions.

Tone of the Heart: Showed slight improvement in 1 case.

Average Duration of Nausea: 2 days.

Average Duration of Vomiting: 1 day.

Patients Improved by Treatment: 1 case showed questionable slight improvement.

Patients Made Worse by Treatment: None.

Summary and Conclusions. 1. The nausea point averages 0.28 cc per pound of body weight.

2. Nausea is usually the first sign of digitalis intolerance.

3. Nausea from digitalis administration is not relieved by atropine.

4. Eight cases of auricular fibrillation and 4 of the 7 cases with regular hearts and evidence of heart failure were improved by treatment. The best drug effect was obtained near the point of nausea.

5. By far the best effects were produced in cases of auricular fibrillation.

6. The development of new rhythm during the digitalis tolerance test is infrequent. Two cases showed occasional premature contractions. One case was a complete heart-block.

7. Little or no effect is produced on the rate of regular hearts by pushing digitalis to the point of nausea.

8. Blood-pressure, both systolic and diastolic, was routinely decreased by pushing digitalis to the point of nausea.

DISCUSSION

Dr. H. A. Hare, Philadelphia: I want to make a protest against carrying the dosage of this drug up to or near the toxic point. I think the promulgation of this idea will lead to a great deal of error if it is generally accepted. Many autopsy studies have indicated that there has been excessive digitalis dosage. I think it will be unsafe in the future to follow the lines of this very sweeping conclusion. In cases of ruptured compensation we may need one or two or three maximal doses up to the point of nausea and vomiting, but there are hundreds of cases of failing heart in which much smaller doses can be given with excellent result. One difficulty may present itself to the student and active practitioner, and that is that sufficient distinction has not been made between severe ruptured compensation, where compensation is suddenly broken down and the condition of the patient is grave, and that form of gradual rupture of compensation in which more moderate symptoms are recognized as a manifestation of the condition. In the first case, doses that are approximately toxic should be given. This custom is followed by many English physicians; they give large doses until the effect is produced and then cut it down. In the second type it is not necessary to give large toxic doses in order to give the heart a rest. There is another factor to be borne in mind: Many of the profession fail to recognize that digitalis is a distinctly dangerous drug in some abnormal conditions of the circulatory system. When there is partial heart-block the giving of massive doses may complete the heart-block. I have seen a patient *in extremis* from the administration of massive doses in this condition. It has been my practice to give 15 to 20 minims of a good tincture to rest the heart over a long period of time. The whole theory of administration of digitalis is the rest and better nutrition of the heart muscle. You cannot rest the heart in twenty-four hours. We have to continue the effect of a massive dose by very many small doses. We put a man to bed to rest his body, and we must also use this idea in resting the heart over a long period of time. Satisfactory results cannot be accomplished in any other way.

Dr. Wood, Philadelphia: These massive doses often produce a very rapid fall in blood-pressure. Another point in question is the prevailing idea that digitalis is to be administered according to pounds of body-weight of the patient, based on the cat-unit scale. I have learned the value of animal experimentation in the laboratory in working out the cat-unit dose, but it is only applicable to a certain extent. In medical practice there is a different element. Individuals do not react according to so many pounds' body-weight, but according to the type of organism. One naturally supposes that an individual of 300 pounds' weight needs more than one of

100 pounds; but there are many cases where there is a moderate degree of dropsy, not very marked, but still in which a dosage of digitalis graduate to scale of body-weight would give rise to erroneous conclusions. There is too great a tendency to impress the profession at large with the idea that massive doses must be given in every case and that each case is not to be handled as an individual entity.

Dr. Brooks (closing): Nausea is the first sign of toxic effect. Just before the point of nausea is reached we usually get the maximum clinical effect. We did not do any harm to any of the patients and in several instances the maximum dosage gave surprising and unexpected benefit. There was very good effect as far as lowering the pulse rate in auricular fibrillation except in one case. The best effect in cases of hypertension was often that produced almost at the point of nausea production.

Dr. Donaldson (closing): This was not a study of digitalis therapy. It was rather a study of the toxic action of the drug. We feared we might develop such complications as auricular flutter or ventricular tachycardia by increasing the irritability of the pacemaker with digitalis. However, very few arrhythmias were noted. We administered 4 cc of tincture of digitalis three times a day to most of the cases until nausea was reached. In estimating the nausea point the patient's weight less edema was used as a basis.

CLASSIFICATION OF HEART PAIN: PRELIMINARY REPORT

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AND

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Heart pain may or may not be a very important symptom. Its general interpretation, however, is so vague and obscure that an attempt has been made by us to work out a classification of practical value in the clinic, where in the past there has tended to be confusion, such as, for example, the partial and unsatisfactory separation of the more severe pain into the so-called angina pectoris and pseudo-angina pectoris.

We have found that more important in analysis of the pain than its position or character is the underlying cause. Therefore our classification is mainly etiological.

Fatigue Pain. Muscle fatigue is without much doubt responsible for the great majority of heart pains. This fatigue pain may be the result of a number of different factors. It may occur in the case of the hypertrophied hearts of chronic hypertension or of aortic regurgitation as a sign largely of left ventricular fatigue. It may occur in the case of the hypertrophied hearts of chronic and well-marked mitral stenosis or congenital pulmonic stenosis as a sign largely of right ventricular fatigue. It may occur in arteriosclerotic heart disease where the coronary arteries are so narrowed permanently that the myocardium is insufficiently nourished with blood, a sign of fatigue of either or often of both ventricles. This does not include the paroxysmal pain of coronary disease—the so-called true angina pectoris. Fatigue pain may also

result from the added effort due to paroxysmal tachycardia or paroxysmal auricular fibrillation or flutter, or permanent fibrillation or flutter where the ventricular rate is not under digitalis control. It may occur with congestive failure no matter what the cause. In fact, taken by itself in the presence of some one of the structural lesions or functional disturbances mentioned above (and in the absence of excessive nervous irritability), this type of heart pain probably should be regarded as the first symptom of the so-called congestive type of failure which may not advance beyond this point.

Nervous Heart Pain. Just how far the heart pain of effort syndrome may be included under the heading of the fatigue type is uncertain. It seems more likely that it should be classed separately, since generally, that is, in the absence of extreme overexertion, it is found in nervous, high-strung individuals, old or young, but more likely in the latter. It is the result of excitement as often as of effort. It would seem to be the result of overaction of the heart in a person with a low sensory threshold.

Both the ordinary fatigue pain and that of the nervous heart vary much in intensity. Generally the pain consists of a precordial ache, but at times it may be so severe that there is a sharp and knife-like stab in the precordia with radiation to the back, left shoulder or axilla, and down the left arm to the finger tips and even to the right side of the chest and the right arm. In the case of the fatigue pain exertion is practically always the exciting factor. In the case of the pain of the so-called nervous heart or effort syndrome, excitement may produce more pain than effort. Rest and digitalis act to relieve or to diminish the likelihood of the fatigue pain, while relaxation, reassurance and nerve sedatives act best in the case of "nervous heart" pain. Nitroglycerin has no beneficial effect in either type—an important point in differential diagnosis between these types and the paroxysmal pain of coronary disease.

Paroxysmal Pain of Coronary Disease. Coronary disease not only exerts an influence in permanently shutting down the blood supply of the myocardium to produce fatigue pain on exertion, but also gives rise to the rather characteristic paroxysmal pain ordinarily called angina pectoris. This may be brought on in susceptible

hearts of older people by any stimulus; whether exertion, excitement, cold air, food in the stomach or gas in the bowels, and when more severe may occur with the individual quiet in bed without obvious exciting factor. It is likely that coronary spasm is the cause giving rise to acute myocardial fatigue, since it is of such paroxysmal nature, without pulse disturbance, and particularly since it is relieved dramatically by the nitrites and not by digitalis. It is important to remember that pain and not disturbed rhythm is characteristic of this condition; we have seen a number of cases of older people with paroxysmal auricular fibrillation wrongly diagnosed and unwisely warned and treated as angina pectoris.

Pain of Coronary Thrombosis. Rapid blocking of a large coronary vessel, almost always thrombosis of a sclerosed artery, is accompanied usually by long-continued heart pain of very severe nature, not relieved by rest, digitalis or the nitrites, and requiring repeated doses of morphine. The seat of the pain is generally precordial or substernal, but now and then it is abdominal, particularly epigastric or right or left hypochondrial, and in such instances it is apt to be confused with acute abdominal conditions such as gall-stone colic or perforation of a peptic ulcer. Recovery may occur in spite of the extreme severity of the pain and the gravity of the condition.

Aortic Pain. In aortic disease of syphilitic origin—that is, luetic aortitis and aneurysm—there is a fairly characteristic dull, high substernal ache sometimes increased to a sharper pain and even radiating, but not paroxysmal. This does not respond to digitalis, rest or nitroglycerin, but tends to melt away under antiluetic treatment. It is likely that potassium iodide has gained some of its great reputation through its action in this type of case. It must be remembered that in luetic aortitis, in addition to the aortic pain, involvement of the coronary arteries may give rise to the typical paroxysmal pain of coronary disease.

Pains of Pericarditis and of Hepatic Engorgement. Finally, there are the transient pains of acute fibrinous pericarditis and the epigastric and right hypochondrial distress of engorgement of the liver, due to congestive cardiac failure, which are generally easily recognized.

In general, it may be said that the more nervous the temperament of the victim of the pain the lower the threshold. Thus in nervous people much less pathology may be back of severe heart pain of whatever sort, but particularly of the paroxysmal coronary disease type, than in stolid people. The recognition of this fact is probably of much importance both in prognosis and in treatment. It must be remembered, too, that the paroxysmal pain of coronary disease may be slight in degree, especially in its early stages. Sometimes pseudo-angina pectoris has at first been diagnosed in such cases, sudden heart death later on showing the diagnostic error.

In general, also, it may be stated that the extent of radiation of heart pain depends largely on the intensity of the pain. The more severe the pain the greater its radiation. Since the paroxysmal pain of coronary disease is apt to be the severest heart pain of all its radiation tends to be greatest. But even in other types of heart pain, relatively unimportant so far as life is concerned, the pain may be severe enough to radiate to the finger-tips.

An attempt has been made to distinguish between right ventricular and left ventricular pain. Rarely this has seemed possible. We have seen two cases with right-sided pain showing at postmortem examination much more involvement (practically occlusion) of the right coronary artery than of the left. All sorts of variations in the position of heart pain and its radiations occur, such as burning sensations in the right or left wrists actually preceding the pain in the thorax. Further study of these variations is necessary.

Finally, mention should be made of the probable coexistence in various cases of pains of different type, for example, the fatigue pain of mitral stenosis and the pain of the nervous heart in a neurotic woman with advanced mitral stenosis, or the aortic pain of luetic aortitis and the fatigue pain of aortic regurgitation, perhaps also the paroxysmal pain of coronary involvement in a middle-aged man with cardiovascular syphilis. In such cases the analysis of the pains is difficult but interesting.

EPENDYMAL CARCINOMA

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Tumors originating from the ependymal cells of the cerebral ventricles are not very common. On the contrary, there are a number of reports of tumors arising from the choroid plexus, especially that of the fourth ventricle, which grow to a relatively large size—3 to 5 cm. in diameter. The plexus epithelium at birth is ciliated. After birth it becomes a secretory membrane, in the cells of which are curious granules. According to Vonwiller, it is not always possible to demonstrate these granules in the cells of the plexus. More than half the ependyma is also ciliated, he found, and he thought that that membrane also secreted cerebrospinal fluid. According to our present conceptions, the fluid is secreted entirely by the cells of the choroid plexus. Brüchanow thinks there is not such a great difference in anatomical structure as in function.

Although there has been some difference of opinion concerning the transformation of glia cells to ependymal cells, and *vice versa*, it appears now to be settled that such transformation does take place. Saxer showed that there was a most intimate relationship between the cells of a solid glioma and the ependymal cells. Cysts within such a tumor were lined with typical ependymal cells, hence he concluded that the cells of the ependyma and the glia can be converted into one another and have the same origin. With this opinion Hart agrees.

Embryologically the choroid plexus cells, the ependymal cells and the glia cells are of the same nature. Tumors may arise from any one of these structures after differentiation postpartum, and

it may be extremely difficult at times to decide in any tumor from which of the differentiated cells the tumor arises.

Ewing calls attention to the relative rarity of tumors arising in and around the choroid plexus. A history of typhoid fever or of coincident tuberculosis has been noted in the published reports. Some authors have mentioned trauma as a possible cause. The tumor is usually single (Cayley and Brown, Saxer, Luick, Muthmann and Sauerbeck, von Wunschheim, Boudet and Clunet, etc.), except in cases of ependymal glioma, when there are regularly multiple tumors (Spiller, etc.). Ewing describes three main structural types: (1) Papillary adenocarcinoma; (2) pavement-cell carcinoma; (3) ependymal glioma. The first group is the usual form of tumor of the choroid plexus, although in the literature simple hyperplasia, producing papillomatous non-malignant tumors, seems to be the most frequent tumor arising from the plexus. The second class also is a plexus tumor, usually beginning in the third ventricle. Its structure resembles common adenocarcinoma with epithelial pearls. The third group is rare; its chief seat is in the fourth ventricle, where it begins as a firm but vascular tumor. "The ependyma of the ventricle is usually the seat of multiple or diffuse, granular or papillary outgrowths, and from such lesions the tumors probably originate . . . alveolar groups of neural epithelium are regularly present in the form of cubical or cylindrical cells, enclosing ill-defined lumina or surrounding capillary blood-vessels. In some cases the cells are very long and cylindrical. . . In very cellular tumors the cells become more numerous, of small size, round or spindle, the fibrils diminish, and a picture resembling round-cell sarcoma may result."

Saxer concluded, from his studies made in 1902, that it was not possible to demonstrate any real differences between the coverings of the cranial cavities and their extensions, the epithelium of the central canal, and the so-called ependymal cells of the spinal cord. The epithelium of the choroid plexus is identical with these cells. Plexus and ependymal epithelium may serve as the origin of similar tumors. In the brain there are pure epithelial tumors which arise either from the ependyma or from plexus epithelium and develop always in the ventricular cavities. They show no trace of formation

of glia tissue, but grow like other tumors of epithelial origin, especially like those of the skin, mucous membrane, etc. These may be carcinoma in the invasive sense, growing into the brain.

At the University Hospital we have had a most unusual tumor, apparently originating in the ependyma of the fourth ventricle, spreading over both lateral ventricles, invading a very short distance into the brain substance and metastasing over the cerebral cortex in the thickened pia mater. Search through the literature has not revealed a tumor growth like this one.

In 1911, Saxer reported before the German Pathological Society a case of carcinosis of the cerebrospinal meninges simulating in its clinical course tuberculous meningitis. The carcinosis was a series of metastases from a primary carcinoma of the pyloric end of the stomach. He said, "In the case which I report here there was found on the membranes of the central nervous system a process which strikingly reminded one of the common form of tuberculous meningitis and also clinically ran a course like that disease."

In the case here reported the resemblance to tuberculous meningitis was so great that when first examined in gross it was thought to be that disease. The excuse for reporting a single case is that it seems to be quite unique and important enough to be placed on record.

Case History.—The case is that of a school-boy, aged thirteen years, who was admitted to the University Hospital, December 11, 1922. The history was obtained from the father. The complaint was blindness, deafness, rapidly increasing weakness and loss of appetite.

Up to about a year ago he appeared to be a normal, healthy boy. He was bright in school and took active part in all boys' games. At the age of twelve years he was in the eighth grade. He had had measles and influenza several years before. The family history was absolutely negative. About a year ago he had some illness which confined him to bed. He had no appetite for food, but drank quantities of milk and water. He passed an unusual amount of urine during this time. About February, 1922, he was under the care of a physician, who reported that he had had periodical maniacal attacks, coming on usually at night. These lasted several weeks, after which he seemed to recover his health. He had lost greatly in weight, but he rapidly regained weight and appeared to be in his normal state of health. Not long after this, about June, he complained of seeing double.

From this time he gradually became blind. About August 1, he began to lose his hearing. His appetite remained good until about five weeks before admission. He became totally deaf. He was very irritable. There were no paralyses and no special weakness of muscles with the exception of the possible weakness of the muscles of mastication. He either could not or would not eat. No headache and no vomiting were present at any time.

On examination by the ward physician the boy was found to be much emaciated, corpse-like. The face bones stood out prominently. The pupils were widely dilated and did not react to light. Accommodation could not be tested. There was marked divergent strabismus of the left eye. The conjunctivæ were injected and were covered with mucopurulent secretion. There were evidently bilateral deafness and blindness. The neck was not stiff. It was impossible to examine the throat. He was excessively irritable. Except for slight probable weakness of the muscles of the lower jaw there were no muscular changes. All deep reflexes were present and equal. Plantar stimulation produced flexion. Kernig's sign was doubtful. It was impossible to make any further neurological examination. Heart, lungs and abdomen showed no abnormalities. The urine was negative. Blood examination showed: Hemoglobin, 95 per cent; red cells, 6,000,000; white cells, 8800. Differential count: Polynuclears, 66 per cent; eosinophils, 1 per cent; small lymphocytes, 4 per cent; large lymphocytes, 29 per cent. The blood-pressure could not be obtained, due to his constant resistance to all forms of examination. At every attempt to examine him he fought with arms and legs and called for his mother or father. Under chloroform anesthesia a lumbar puncture was done. The fluid was clear and not under abnormal pressure; there was a great increase of solids and 800 cells per cu. mm. The reaction for glucose was absent. The Wassermann reaction was negative.

Stereoscopic *x*-ray plates of the head showed increase in the vertical diameter. There was marked prominence of the frontal sinuses. The depressions for the Pacchionian bodies were quite distinct. A "lime density" shadow was seen at or near the situation of the pineal gland. The sella was normal. Attempts to examine the eye-grounds were unsuccessful.

During the four days he was under observation he had no fever, the pulse was variable but not slow (from 100 to 120), the respirations were 22 to 25 per minute. There was a suggestive bilateral Kernig's sign and a slight stiffness of the neck, but no localizing signs over the body elsewhere. He developed twitchings of the head, the pulse and respirations rapidly increased, and he died on December 14, four days after admission.

Autopsy was held on December 15 in the department of pathology. The report is as follows:

Pathological Diagnosis. Ependymal glioma of the carcinomatous type primary in the region of the fourth ventricle. Extension through the ventricles, basal meninges, neighboring portions of the brain and hypophysis. Older leptomeningitis. Moderate internal hydrocephalus. Thymicolymphatic constitution (hyperplastic thymus, generalized hyperplasia of the lymph nodes with exhaustion of the germ centers, hypoplasia of the adrenals). Hypoplasia of the genitalia. Infantile testes with fibrosis. Lipolipoidosis of the liver.

The body is that of a boy rather small for his reported age and measures 140 cm. in length. The head is large, especially in the upper portion posteriorly. The eyes are deep set, the eyebrows slightly overhanging and the interocular space is broad across the bridge of the nose, suggesting somewhat the lateral displacement found in internal hydrocephalus. The pupils are dilated, symmetrical and equal. The body is decidedly emaciated. Rigor mortis is present. The skull-cap is of about normal thickness. There are several deep pits on the inner table for Pacchionian granulations. The dura is not unusually adherent. The longitudinal sinus is empty anteriorly; a small amount of fluid blood posteriorly. The meningeal vessels are moderately congested. The basal vessels are nearly concealed in adhesions and thickened inner meninges. They show no thrombosis or sclerosis. The inner meninges show everywhere well-marked edema and diffuse opacity. This increases in density toward the vertex. No areas are found suggesting tubercles. The process appears to be in the healing stage. On lifting up the brain there is increased fluid at the base. Both optic nerves up to the point where they enter the optic foramina and the optic tract, in the region of the chiasm, are found to be enormously enlarged and very soft. Upon turning the brain over this tissue completely collapses into the interior of the brain, but upon slight pressure abundant thick, turbid fluid wells up from the region of the optic tract. On section of the brain there are congestion and edema. All the ventricles are somewhat dilated and filled with turbid fluid like that described at the base. The ependyma is everywhere clouded, roughened, in some areas having a mammillated appearance with heavy flakes of exudate which seem to extend slightly into the cerebral substance. No definite tumor mass is anywhere seen. The choroid plexus is everywhere covered by similar exudate and is bound down by numerous adhesions which become quite heavy in the region of the pineal gland. The gland cannot be positively identified in the midst of the adhesions. Just posterior to its situation is a calcareous mass about 4 mm. in diameter, mulberry-like. This easily shells out from the surrounding tissue. The cerebral ganglia, peduncles, cerebellum, pons and medulla show no abnormalities except for the thickened meninges previously described. The hypophysis is small and appears atrophic as if from pressure. The basal sinuses con-

tain fluid blood. The cranial nerves, except the second, seem normal. The ethmoid cells contain purulent secretion, but show no necroses.

The thymus is large, the right lobe 6 cm. and the left lobe 8 cm. in length. The heart shows no abnormalities. The lungs are free from adhesions. At the apex of the left lung is a small anthracotic scar suggesting healed tuberculosis. On cut section the lungs show edema and hypostatic congestion. The spleen is small. On section the lymphoid tissue is relatively scant while the stroma is increased. The liver is about normal in size. The capsule is smooth. Beneath the capsule there are numerous small, yellowish areas varying from pin-point to pin-head size. None show central caseation. They appear to be areas of fatty infiltration rather than tubercles. On section there is slight increase in fat.

Other abdominal organs are without interest. All the abdominal lymph nodes are hyperplastic and congested.

The kidneys reveal slight congestion and cloudy swelling. They are about normal in size.

Microscopical Examination. The changes in the thoracic and abdominal organs are of no special interest. They consist mainly of atrophic and fatty infiltration. No evidence of actual inflammation or of cloudy swelling is seen. The lymph nodes and adrenals show hypoplasia.

The meninges over the convexity show a marked thickening, edema and congestion. There is moderate small-celled infiltration in places, presenting the picture of a nearly healed leptomeningitis. In the thickened meninges occasional small groups of neoplasm cells are found. Toward the basal meninges the neoplastic infiltration becomes more and more marked until finally the meninges are replaced by a diffuse neoplastic growth in which the original vessels of the meninges are still preserved. Many of these vessels show perivascular lymphocytic infiltration. There are, however, some new, small bloodvessels throughout the tumor mass. Along the surface of the brain the neoplasm infiltrated into the brain substance in varying depths. This infiltration is particularly along the perivascular lymphatics, so that the cords of the neoplasm appear in the outer layers of the brain tissue surrounding the original bloodvessels, practically all of which show inflammatory infiltrations.

The cerebral hemispheres show congestion, but no neoplasm except toward the base and toward the lateral ventricles. The lateral ventricles show, for the greater part, a replacement of the ependyma with a tumor mass varying from $\frac{1}{2}$ to $\frac{2}{3}$ mm. in thickness, showing a distinct irregular granular surface. The majority of the bloodvessels in the neighborhood of the ventricles show perivascular mantling with lymphocytes.

The choroid plexus is infiltrated with the neoplasm. Many of the vessels show perivascular infiltrations of lymphocytes and even polynuclears. There are several collections of a fibrinous exudate containing many polynuclears on the surface of the neoplasm.

There are numerous large calcareous concretions in the region of the pineal gland and on its surface there are areas of neoplastic infiltration, although the body of the gland is not infiltrated by the neoplasm. The small calcareous nodule just back of the pineal region consists of neoplasm with numerous sand bodies conglomerated into larger masses.

The anterior lobe of the hypophysis is about normal in size. It shows acute passive congestion. Very few eosinophilic cells are seen. The majority of the cells are basophilic. There is no neoplasm in the anterior lobe. The intermediate lobe shows a number of colloid spaces, but both intermediate and posterior lobes are infiltrated throughout with the neoplasm.

The neoplastic thickening of the ependyma and the neoplastic infiltration into the brain substance increases toward the pons and toward the fourth ventricle, the growth being most marked in the pons, where it infiltrates nearly entirely through the substance of the pons. In some places in the ventricles the growth of the neoplasm is subependymal and there is a striking resemblance between the ependymal cells and those of the neoplasm in such areas. The neoplasm, for the greater part, consists of large polymorphous cells, many of which are round, others oval, with abundant basophilic cytoplasm, the cytoplasm in many cases staining as heavily as the nucleus. In some areas the cells are distinctly cuboidal or even low columnar. Many of the cells have polar processes. The nuclei, for the greater part, present a distinct nucleolus with a lighter zone about it and the chromatin granular and not compact. Many of the cells are polynuclear, two or three nuclei. They have a more distinctive epithelial than connective-tissue character. There is no connective-tissue stroma, but a very scanty stroma made up of neuroglial fibrils. In the large mass of the tumor there is no new formation of bloodvessels. The growth surrounds the original bloodvessels in mantling columns, giving a false appearance of a perithelioma. In all cases these original bloodvessels show thickened and inflamed walls. There is no hemorrhage into the growth, no areas of necrosis and the surrounding brain tissue shows only changes of pressure. The appearances are those of an ependymal glioma of the carcinomatous variety, the carcinoma being of a more medullary type than the adenocarcinoma type that has been seen in some cases.

The origin of the tumor was probably in the fourth ventricle. Although there was no macroscopical tumor there, the microscopical appearances led to the belief that in the choroid plexus the tumor started. All of the tumors of the fourth ventricle reported in the literature were of macroscopical size, several being 3 to 5 cm. in diameter. (Mallory, Boudet et Clunet, etc.) Only rarely were multiple tumors found. Hart, in 1910, searched the literature and

analyzed the cases of carcinoma of the ependyma. He could find but 2 cases which would stand his criticism. Malignancy, according to him, consists in destructive growth and formation of metastases. One of the 2 cases was a multiple alveolar carcinoma arising from the ventricular ependyma (Späts); the other (Kölpin) was a multiple papillomatous growth also apparently arising from the ependyma. To these 2 cases Hart adds 1 of his own. This was a woman, aged fifty years, who had a tumor, the size of a goose egg, projecting into the centrum semiovale and another small sessile tumor lying upon the left optic tract at the base of the brain. There were enlarged submaxillary glands. The tumor arose from ependyma cells (glia tissue). He considered the metastases to the glands to be of the same nature. He called it carcinoma of the ventricular ependyma.

I have been unable to find in the literature since 1910 any case which at all resembles the one here reported. No tumor like this has been seen in over 3000 autopsies in the pathological laboratory of the Ann Arbor University. Certain interesting features are worthy of mention: (1) There was irritation from a chronic leptomeningitis. This probably was the result of the illness the boy had in the spring of 1922, which, in the light of what was found at autopsy, may have been endemic cerebrospinal meningitis. It seems highly probable that the chronic irritation initiated the growth of the ependymal cells. So little is definitely known of the origin of lawless cell growth that in all tumors chronic irritation is given as the most important single causative factor. Here the chronic inflammation of the meninges is definitely demonstrable, both macroscopically and microscopically. Although there was no evidence of inflammation in the growth, it may well be that this evidence was obscured by the proliferation of the tumor cells. I think we are justified in assuming that chronic leptomeningitis had an intimate relationship to the origin of the growth. (2) Although the seat of the chronic irritation was over the hemispheres, the tumor was of ependymal origin and seemed to be metastasing in the leptomeninges over the convexity of the brain. This seems to be correct, although cells were not followed from the base over the hemisphere. Only here and there were single cells

or groups of several cells found which in size and staining characteristics were identical with the cells of the tumor. The only path which seemed possible for these cells to travel was the lymphatics. It is possible to consider these as metastasing areas, and possibly, also, had the child lived there might have been metastases beyond the cranial cavity. (3) There were no other metastases anywhere in the body. (4) The tumor was truly invasive, as it can be seen dipping into the brain substance. (5) It did not have its origin in the choroid plexus. The plexus appeared everywhere normal.

A most interesting point is the history of great thirst and polyuria. Was this due to irritation of the pituitary gland—a diabetes insipidus? The symptoms ceased as he recovered from his attack and apparently never returned. The microscopical examination of the hypophysis gave no information on this point except to reveal infiltration with tumor cells in both intermediate and posterior lobes. It is possible, I presume, that the destruction of the posterior lobe by the tumor caused the symptoms to disappear, or that the small size of the gland revealing pressure atrophy so disturbed the gland that it ceased spontaneously to produce the substance responsible for the polydipsia and polyuria.

The clinical signs were confusing. There were total blindness and deafness, with retention of voice. It was impossible to test smell and taste. There were no localizing symptoms; no fever; no actual signs of inflammation at the base of the brain. We had a process which we considered was widespread and had produced increased intracranial tension. Like Saxer's case, it has some similarities with tuberculous meningitis. A diffuse tumor with hydrocephalus was hazarded as the most probable change which could produce the symptoms and signs.

Pathologically the tumor had the appearance of the exudate of tuberculous meningitis, except that it remained adherent to the lateral ventricles. The ventricular fluid contained large numbers of tumor cells. It had a slightly granular appearance, but in no sense was it ependymitis granularis as defined by Brüchanow, Margulis and others. True ependymitis granularis is localized inflammation of the glia producing small granulations just beneath

the ependymal lining. They are firm, slightly raised above the surface and are usually denuded of epithelium. They are found, according to Margulis, in many diseases of the brain and even in normal persons. In fact, Saltykow, who looked upon the granulations as a true inflammation of the glia tissue, found the granulations present in every one of 120 mentally normal persons between the ages of seventeen and eighty-four years. Margulis saw the granulations with the naked eye in only 6 of his 11 cases. He described them as minute ball-like or cone-shaped new growths of glia looking not unlike sago grains. There was great similarity in the microscopical appearance in all the nodules. There was a central and a peripheral zone. The former consisted of a network of glia with glia nuclei in its meshes. The peripheral portion is formed of a thin layer of glia cells with fewer nuclei; the whole is covered by ependymal cells. The process is active and progressive. The origin is congenital. He considers that it occupies a mid-ground between chronic inflammation and new growth and belongs to the congenital glioses of the central nervous system.

Saltykow states that there is no epithelium over the granulations —in other respects, he agrees with Margulis.

The microscopical examination of the tumor gives the impression of a sarcoma. The cells are packed together with very little stroma, and finger-like processes composed of solid masses of cells dip for a short distance into the brain. However, the character of the cells is not that of cells of connective-tissue origin. There are areas throughout the growth in the lateral ventricles where the ependymal epithelium seems to be intact and the tumor cells appear to lie between the ependyma and the brain substance. The remnants of epithelium are composed of rather flat or very low cuboidal cells and the appearances of the sections with the epithelium torn and laid back here and there seems to confirm the supposition that the tumor has infiltrated between the ependyma (subependymal) and the brain.

Summary. A case of a peculiar ependymal carcinoma, in a boy thirteen years of age, is described. Chronic leptomeningitis may have been a factor in originating the growth. The symptoms resembled somewhat those of tuberculous meningitis, but were

unusual in that there were bilateral blindness and deafness, no paralyses and no striking evidences of irritation at the base of the brain.

In a search over the literature no similar case has been found.

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PHYTO-PHARMACOLOGY AND SOME OF ITS CLINICAL APPLICATIONS

(ABSTRACT)

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During the past few years the author has been carrying on a comparative study of the effects of various drugs and toxins on animal and plant protoplasm. It was soon found that plant tissues often react very differently from animal tissues in respect to the action of various substances. Thus, Macht and Livingston,[1] in connection with a study of cocain and its decomposition products, have shown that whereas cocain is very toxic for animals, the same alkaloid is much less toxic for plants; on the other hand, sodium benzoate, which is practically innocuous for animal tissues, was found to be extremely toxic for plant tissues. These observations suggested that possibly plant tissues or plant preparations might be more suitable as test objects for certain animal toxins than ordinary animal tissues. Accordingly, various studies along these lines have been begun by the author with various collaborators. Two animal products of metabolism have been especially studied up to the present time. In the first place the author applied "phyto-pharmacological study," as it might be termed, to an investigation of a "menotoxin" or menstrual poison. In the second place, phyto-pharmacology was applied to the study of various blood diseases, and more particularly to *pernicious anemia*.

The method employed in the study of both conditions was the growth of seedlings of the *lupinus albus*. This lupine is a very

[1] Jour. Gen. Physiol, 1922, iv, pp. 573–584.

hardy one and very suitable for quantitative study, inasmuch as its single straight root can be very accurately measured in length.

The method employed by the author and his collaborator, Miss Lubin, for the study of menotoxin, was as follows: Seedlings of *lupinus albus* were grown in a perfect nutrient medium (Shive solution) and the rate of growth of the single straight, well-defined root was measured to within $\frac{1}{2}$ mm. Similar seedlings were grown simultaneously and under exactly the same conditions in Shive solution containing a definite amount, usually 1 per cent of normal blood serum, and on other occasions exactly the same kind of experiments were performed with solutions containing blood serum obtained from a vein of menstruating individuals. Whenever possible, normal and pathological blood was obtained from the same subjects. The effect of normal serum on the growth of seedlings as compared with normal Shive solution was determined, and in a similar way the effect of menstrual serum on the growth of seedlings was ascertained. It was found that while the average growth of the seedlings in a 1 per cent solution of normal blood serum in Shive solution gave about 75 per cent of growth as compared with the normal Shive, a similar solution of menstrual serum affected the seedlings in a much more toxic way. This toxicity expressed itself in two ways: In the first place the absolute growth in the length of the roots was much less (on an average about 50 per cent) as compared with the normal seedlings. In the second place the rootlets no longer grew in a perfectly straight direction but were curled and distorted in various ways. Numerous experiments repeatedly performed in the above way with numerous samples of sera from normal and menstruating subjects as compared with normal ones. The greatest toxicity was usually found at the beginning of menstruation and was demonstrable even during the premenstrual period of a day, before the actual onset of the catamenial flow, growth in such cases being as low as 30 per cent of the normal.

Similar experiments were made with samples of *saliva* obtained from normal and menstruating subjects, and difference in toxicity was conclusively demonstrated in the case of that secretion also. It was also found that what we may call the "menotoxin" was

present likewise in the *red blood cells*, and some very striking experiments revealed the presence of the same menotoxin in the *skin secretion* of menstruating individuals. Experiments are in progress with a view of ascertaining more intimately the chemical nature of the menotoxin. Various glandular extracts, such as ovarian, corpus luteum, thyroid suprarenal, pituitary, etc., have been examined and more definitely known chemical compounds have also been studied.

The growth and development of *lupinus albus* was also studied under the influence of sera from patients exhibiting various blood diseases. Blood serum from patients suffering from secondary anemias of various kinds, myelogenous leukemia, lymphatic leukemia, Hodgkin's disease and pernicious anemia were used in these experiments. It was found that the serum of patients affected with pernicious anemia exerted a very different effect on plant protoplasm from that of other sera. In a large number of cases of pernicious anemia obtained from various sources the serum invariably exhibited very great toxicity, often inhibiting the growth of *lupinus albus* to as little as 20 per cent as compared with the normal increase in growth of control preparations. Bloods from secondary anemias were not found to be toxic at all, and it was surprising to find that the serum from leukemia patients was not at all toxic. Serum from Hodgkin's disease exhibited quite a marked toxicity, but was not as poisonous as pernicious anemia. The author has begun a study of various other clinical conditions by the use of the above phyto-pharmacological method, the results of which will be published in due time.

SOME OBSERVATIONS ON THE PHENOLTETRACHLORPHTHALEIN TEST AS A MEANS OF DETERMINING LIVER FUNCTION*

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Since the publication of the work of Rowntree, Hurwitz and Bloomfield,[1] in 1913, advocating the use of phenoltetrachlorphthalein as a test for liver function, considerable attention has been directed to this test. Inasmuch as the dye was first collected through the feces, many discrepancies were noted as to its determination by various observers, so that Whipple,[2] McLester and Frazier,[3] and Kahn and Johnston[4] report unfavorably concerning it, while Sisson,[5] Chesney Marshall and Rowntree,[6] and Krumbhaar,[7] on the other hand, consider it of considerable value as a means of determining liver function.

On account of the great variations in results, McNeil[8] recommended the collection of the dye through the duodenal tube, and Aaron, Beck and Schneider,[9] as well as Piersol,[10] have since advocated this method. Following the plan advised by Aaron and his co-workers, we have given 169 single injections of this dye to 93 individuals, utilizing the stable solution recommended by them.

Technic. The technic in carrying out the test is as follows: Immediately before injecting the dye, the duodenal tube, being held *in situ*, with a strip of adhesive wrapped around it beyond the third mark and the free end of the adhesive strapped on the cheeks, the patient is given two or three glasses of ice-cold water

* From the Gastro-enterological Clinic of the Department of Medicine, University of Maryland.

to drink. In nervous hypersensitive patients hot water should be introduced very slowly through the duodenal tube. The object of the water is to stimulate the gall-bladder to contract as well as to relax the sphincter of Oddi and to provide a free flow through the tube. When this flow is established 1 cc, containing 75 mgm. of the disodium salt of the phenoltetrachlorphthalein, is diluted with 5 cc of sterile physiological salt solution and injected intravenously. It is better, in our experience, to detach the needle from the syringe and insert it first into the vein as the color of the dye makes it difficult to note the return of the blood through the needle. A bit of gauze is held firmly around the needle when it is withdrawn to prevent any return leakage, as the phthalein is extremely irritating to the subcutaneous tissues.

Previous to utilizing this method of dilution, considerable irritation of the arm resulting from a leakage of the dye through the vein or the escape of even as small an amount as a drop into the subcutaneous tissues was produced and several instances of thrombosis resulted from the action of the concentrated dye on the walls of the vein at the site of the injection; but since using sterile salt as a diluent we have not noted a single untoward effect.

The flow from the duodenal tube is allowed to run by gravity into successive porcelain basins, containing 2 cc of a 40 per cent sodium hydrate solution to secure the time of maximum appearance of the dye. If the flow through the tube ceases the patient should be given more water, and in some cases where there is no flow of bile, by the use of the water 3 cc of a 10 per cent hydrochloric acid solution in 30 cc of water should be injected through the duodenal tube.

Due to the possibilities of error we have not followed the method advocated by Piersol—that is, the estimation of the output of the dye—but have limited our studies to its time appearance, which, according to our experience, has been extremely constant.

The usual cause of failure to obtain the dye in a normal individual is due either to not having the duodenal tube in proper position or to the absence of a free return flow of water through the tube.

The following table illustrates the time of excretion of the dye in normal and pathological cases:

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
1	1	B.	2- 4-22	21	M.	Achylia gastrica	7 min.	9	Constant.
	2		1-31-22				8	12	
2	3	S.	3-15-22	25	M.	Catarrhal jaundice (subsiding)	8	30	
	4		3-17-22				14	30	Faint.
3	5	S.	3-21-22	38	M.	Chronic cholecystitis	8	14	
	6		5-18-22				12	15	
4	7	F.	3-22-22	55	F.	Paresis (early)	8	11	
5	8	C.	2-20-22	26	..	Typhoid relapse	9	11	
6	9	B.	12-22-21	45	M.	Cholelithiasis, chronic cholecystitis	None in	60 min.	
	10		12-23-21				None in	75 min.	
	11		12-24-21				None in	90 min.	
	12		12-28-21				18	24	
	13		1- 5-22				8	12	
7	14	A.	1-25-22	40	M.	Neurosis	20	25	
	15		2- 3-22				9	15	
8	16	C.	3-23-22	35	M.	Gastric neurosis	9	14	
9	17	G.	1-29-22	65	F.	Chronic cholecystitis, cholangitis and gall-bladder calculi	9 min.	13 min.	
	18		2-15-22				15	16	
10	19	D.	5-10-22	55	F.	Chronic cholecystitis, adhesions and morphinism	10	14	
11	20	D.	4-24-22	15	M.	Acute catarrhal jaundice	10	14	
	21		4-26-22				10	16	
12	22	H.	3- 8-22	28	M.	Psychoneurosis	10	12	
	23		3-10-22				10	16	
13	24	Q.	3- 6-22	58	M.	Psychoneurosis	10	10	
14	25	P.	5- 7-22	38	M.	Malnutrition, visceroptosis, neurosis	10	14	
15	26	S.	4-25-22	55	M.	Arteriosclerosis and myocardial insufficiency	10	15	
16	27	T.	.....	14	M.	Epilepsy, achylia nervosa	11	14	
17	28	K.	3-29-22	35	M.	Cancer of rectum with abdominal metastases	12		Faint.
18	29	H.	5- 5-22	55	M.	Chronic cholecystitis, gastric neurosis	10	14	
	30		5- 7-22				15	6	
	31		5- 9-22				10	14	
	32		5-15-22				15	45	
	33		5-16-22				15	18	
	34		5-20-22				19	22	
	35		5-22-22						
	36		5-31-22				20	25	
	37		5-24-22			Given adrenalin ℳx	18		
	38		1-11-22	40	M.	Syphilis, secondary	16	18	
19	39	G.	1-15-22				10	14	
20	40	B.	3- 3-22	..	..	Posteclampsia	11 min.	15	
21	41	T.	1-11-22	42	M.	Chronic cholecystitis, eczema	14	20	
	42		1-17-22				13	13	Faint.
	43		1-14-22				12		
22	44	C.	4-12-22	30	M.	Acute cholecystitis	12	18	
23	45	B.	3-27-22	60	F.	Syphilis of liver	11	12	
	46		5- 8-22				25		
24	47	A.	2- 9-22	35	M.	Cardiac decompensation (Chronic passive congestion. Autopsy)	13	16	
25	48	A.	1-13-22	45	M.	(After operation for stones)	15	18	
	49		1-16-22			Gall-bladder draining	12	16	
	50		1-23-22				11	14	
26	51	P.	1-12-22	45	F.	Chronic polyarthritis	20		
	52		1-16-22				13		
	53		1-18-22				13		
27	54	A.	1-27-22	48	F.	Neurosis	14	30	
	55						13	23	
28	56	W.	2- 6-22	45	M.	Gout	13	26	

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
29	57	W.	12-24-21	25	M.	Addison's disease	20	22	
	58		12-27-21				12	14	
	59		1-11-22				10	16	
30	60	R.	1-18-22	26	F.	Pregnancy (8 mos.)	13	15	
31	61	W.	2-10-22	30	F.	Posteclampsia	13	16	
32	62	S.	1-12-22	40	F.	Cholecystitis	12		
	63						20		
	64						12		
	65						20?		
	66						21		
33	67	C.	5- 9-22	30	M.	Epilepsy, polycythemia	12	14	
34	68	A.	3- 9-22	25	M.	Bichloride poisoning	15	17	
35	69	B.	1-26-22	48	M.	Cancer stomach (inoperable)	15	18	
36	70	K.	3-24-22	40	M.	Normal	14	16	
	71		3-28-22				19	19	
37	72	L.	1-18-22	32	F.	Pregnancy (8 months)	14	18	
38	73	H.	3-19-22	42	F.	Cholelithiasis	15	25	
	74						14	25	
39	75	M.	4- 3-22	24	F.	Subacute cholecystitis	15	16	
40	76	M.	3- 3-22	50	..	Cholecystitis and cholelithiasis	15	18	
41	77	P.	2-18-22	50	F.	Eclampsia (3 days after delivery)	15	16	
42	78	T.	3-30-22	38	F.	Hyperacidity, cholecystitis	15	18	
43	79	T.	3- 4-22	38	F.	Chronic cholecystitis	16	18	
44	80	M.	3- 1-22	40	F.	Aortic aneurysm	18	35	Faint.
45	81	J.	1-20-22	55	M.	Chronic alcoholism	17	19	
	82		1-21-22				14	16	
	83		1-24-22				15	17	
46	84	C.	1-17-22	29	M.	Diabetes (severe)	16	19	
47	85	B.	4- 6-22	65	F.	Cancer pancreas and liver (non-obstructive)	16	45	
48	86	F.	3- 1-22	40	F.	Visceroptosis	18	20	
49	87	B.	1-17-22	22	M.	Syphilis (secondary)	17	19	
	88						19	22	
50	89	S.	1-17-22	18	M.	Rupture of liver	19	21	
51	90	A.	1-17-22	32	M.	Thyrotoxicosis	12	16	
	91		1-19-22				22		
52	92	S.	1-14-22	45	M.	Appendicitis	19	22	
53	93	B.	2- 6-22	36	M.	Typhoid (convalescing)	21		
	94		2- 8-22			Acute cholecystitis	14		
	95		2-20-22				15	30	
	96		2-23-22				20	20	
54	97	S.	12-23-21				20	22	
55	98	S.	12-24-21	58	M.	Malnutrition	20	22	
56	99	W.	3-23-22	70	M.	Chronic cholecystitis with cholelithiasis	10	22	Intermittent.
	100		3-17-22				14	25	
	101		3-21-22				15	16	Faint.
	102		3-27-22				12	16	
57	103	Y.	3-12-22	26	F.	Chronic cholecystitis, neurosis	20	20	Faint.
58	104	C.	1-10-22	11	F.	Epilepsy, hyperpituitarism	21		
59	105	A.	1- 5-22	65	M.	Pancreatitis, cholecystitis, cholelithiasis	21	25	
	106						20	26	
	107						22	27	
60	108	B.	2-16-22	70	M.	Chronic cholecystitis	22	22	Faint after 22 min.
61	109	H.	2- 8-22	45	M.	Chronic cholecystitis	22	26	
62	110	H.	.....	62	M.	Chronic cholecystitis, cholelithiasis	23	33	
	111		3-25-22				23	33	
63	112	S.	2-10-22	55	M.	Diabetes (moderate)	25	25	Faint.
64	113	W.	2-24-22	3	M.	Hepatitis	0 in ½ hr. (subcutaneously).		
65	114	C.	5- 1-22	55	M.	Cirrhosis of liver (fatal)	0 in 120 min.		
	115						0 in 60 min.		
66	116	W.	3-21-22	45	F.	Chronic pancreatitis, hydrops of gall-bladder	0 in 120 min.		
	117		3-19-22				0 in 60 min.		

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
	118		4–12–22				0 in 50 min.		
	119		2– 4–22				0 in 240 min.		
	120		2–20–22				0 in 75 min.		
	121		2–24–22				Faint in 120 min.		
	122		2–17–22				0 in 75 min.		
67	123	W.	12–23–22	58	M.	Chronic pancreatitis	45	45	
68	124	S.	2– 1–22	25	F.	Eclampsia (1st test while in eclampsia, just after convulsion; last test after recovery)	0 in 40 min.		
	125						0 in 180 min.		
	126						195 faint		
	127						18		
69	128	T.	1–10–22	70	F.	Cancer head pancreas with obstruction	0 in 2 hrs.		
70	129	S.	1–11–22	50	F.	Cancer head pancreas, cholecystgastrostomy	0 in 2 hrs.		
71	130	W.	2–13–22	3	M.	Cirrhosis of liver	0 in 120 min.		
	131		2–21–22				0 in 45 min.		
	132		3 –2–22				20 very faint	90	until 45 min.
72	133	S.	2 –7–22	38	F.	Cholelithiasis, acute cholecystitis	21	24	
	134		2–20–22				18	22	
	135		2–22–22				24 faint	24	
	136		2–27–22				18		
	137		2–14–22				21	24	
	138		3– 2–22				18	20	
73	139	G.	1–11–22	45	M.	Cancer stomach	21	28	
74	140	L.	5–13–22	74	F.	Stone in common duct	0 in 40 min.		
	141		5–15–22			Starvation (4 to 8 days)	0 in 40 min.		
	142		5–16–22				19	35	Faint.
	143		5–17–22				17	20	Intermittent.
75	144	B.	2–25–22	45	F.	Stone in common duct, jaundice	19	29	
	145		3– 8–22						
	146		3–20–22				40		
	147		3–21–22				14	47	Intermittent.
76	148	B.	1–21–22	73	M.	Stone in common duct, cholangitis (severe)	19	19	Very faint.
	149		1–22–22				35	78	Very faint.
	150		1–23–22				60	60	Very faint.
77	151	B.	2–13–22	46	F.	Cholelithiasis, cholecystitis, syphilis of liver	25 single spurt at 25, none after.		
	152		5–18–22				70 faint, intermittent pale bile.		
78	153	G.	4– 6–22	55	..	Stone in common duct	36	36	Faint, intermittent.
79	154	M.	4–20–22	44	F.	Stone in common duct	40		
80	155	S.	3–13–22	30	M.	Cirrhosis of liver, syphilis	45 faint	120	Normal.
81	156	B.	4– 1–22	52	M.	Cancer head pancreas (obstructive)	0 in 3 hrs.		
82	157	T.	4–13–22	30	M.	Salvarsan jaundice	0 in 75 minutes		bile flows freely.
83	158	B.	4–21–22	58	M.	Cancer pancreas	0 in 3 hrs.		
84	159	B.	6– 2–22	18	F.	Pregnancy, cholelithiasis	18	34	
85	160	C.	5–29–22	40	F.	Intestinal toxemia	45 faint		
	161		5–26–22			Adrenalin ℥ V (h)			
86	162	S.	5–30–22	35	M.	Dysentery	20	25	
87	163	R.	5–22–22	50	M.	Cholelithiasis	16	28	
88	164	W	5–23–22	21	M.	Neurosis	15	20	
89	165	G.	5–20–22	26	F.	Peptic ulcer	20	20	Intense.
90	166	J.	6– 5–22	40	M.	Chronic cholecystitis	13	35	Intermittent.
91	167	G.	6– 6–22	30	M.	Biliary stasis	10	25	Intermittent.
92	168	H.	6– 6–22	30	M.	Biliary stasis	10	55	Intermittent.
93	169	Dr. B.	6– 6–22	50	M.	Atrophic cirrhosis	0 in 3 hrs.		

As a result of the study of our 93 cases, the following observations are noted:

Method of Administration. The dye should only be utilized intravenously; when given subcutaneously once and intramuscularly twice to a normal individual having an excretion time of fifteen minutes there was no appearance in two hours, when the tube was withdrawn. Preceding the administration of the dye by a non-surgical biliary drainage has apparently no effect on the time of excretion.

Daily Variation in Normal Individuals. A reference to the table in which the test was made in 20 normal individuals (in every instance more than once) reveals variations of only a few minutes from day to day in the time of appearance of the dye. A longer variation than this, we consider, indicates either imperfect technic or some pathological affection.

Effect of Starvation. Following a six-day or an eight-day fast in the same patient the time of excretion was nineteen and seventeen minutes respectively, indicating that starvation has but little direct influence upon the appearance of the dye.

Age. The variations of age of the individuals in our table ranged from thirty-seven months to seventy-two years, but both of these extremes were in pathological cases. The average of the normals reveals practically no variation according to age.

The average rate of excretion of all normal cases is 13.8 minutes.

Sex. In 56 males the average time of excretion was 13.7 minutes, and in 37 females 13.9 minutes. There is therefore no difference attributable to sex. Aaron reports an average of 17.2 minutes in 10 normal individuals, utilizing the same quantity of dye, while Piersol's results, using double the quantity in 15 normal individuals, were lower than ours by several minutes.

Pregnancy. Uncomplicated pregnancy in 8 instances showed an average excretion of fourteen minutes, viz., somewhat below the average normal.

Diabetes. There were 2 instances with an average excretion time of twenty-five minutes and sixteen minutes, averaging 19.5 minutes. There appeared to be no relation as to the severity of the disease to the rate of excretion of the dye.

Epilepsy. In 3 cases of epilepsy the readings were twenty-one minutes, twelve minutes and eleven minutes. The average was 14.9 minutes.

Psychoneurosis. The average excretion of 9 cases was 12.8 minutes.

Toxemias. Three cases of eclampsia examined immediately after the convulsive stage averaged fifteen minutes. A fourth case was done during the stage of convulsions and repeated four times as the patient improved. In this case the results were parallel with the condition of the patient. At first there was no excretion in forty minutes, when the patient had a convulsive seizure and removed the tube; at the second trial there was no excretion in one hundred and eighty minutes; in the third there was just a trace in one hundred and ninety-five minutes, and in the last, when the patient's symptoms had cleared up, the time of excretion was normal, namely, eighteen minutes. In a case of bichloride poisoning three days after the patient had taken 12 grains there was no delay in the initial appearance of the phthalein; the patient, however, had but the mildest symptoms at the time of the examination.

Malnutrition. The average appearance in 2 instances was fifteen minutes.

Catarrhal Jaundice. In 2 subsiding cases the average was 10.5 minutes.

Endocrine Disturbances. A case of Addison's disease averaged fourteen minutes for three tests; 1 of hyperpituitarism with epilepsy was twenty-four minutes; 1 of thyrotoxicosis averaged seventeen minutes.

Syphilis. In 2 cases of secondary syphilis the average secretion was noted in sixteen minutes in four examinations. Several cases of syphilis with complications are summarized in the accompanying table.

Acute Infections. Five tests in 2 typhoid fever patients averaged 15.8 minutes.

Cholecystitis with Cholelithiasis. The rate of excretion in 40 cases of cholecystitis averaged seventeen minutes.

Stone in the Common Duct with Jaundice. The average rate of excretion was twenty-eight minutes in 9 cases. In 5 others there

was no excretion whatever of the dye during the entire period of examination.

Cancer of the Liver. In a case which came to autopsy two days following the test the time of excretion was twenty-five minutes; in another instance it was forty-five minutes.

Atrophic Cirrhosis of the Liver. In 2 instances of this affection there was no excretion in two hours, or in forty-five minutes respectively, when the tube was removed.

Cancer of the Pancreas. In 1 case there was no excretion in three tests in two hours; in the second the average rate was forty-five minutes.

Jaundice following the Use of Salvarsan. In 1 instance there was no excretion in seventy-five minutes.

Cardiac Disease. In a single case of myocarditis the rate of excretion was eighteen minutes; in 1 of chronic passive congestion, two weeks before death, it was thirteen minutes.

From the examinations made by us, as well as those by Aaron and others, regarding the phenoltetrachlorphthalein test for liver function, we believe the following conclusions may safely be drawn:

1. The phenoltetrachlorphthalein test is a valuable means of determining liver function.

2. In order to obtain reliable results the technic in performing the test must be carefully carried out in every detail. On this account the preparation utilized must be stable and free from all deterioration. The tube must be *in situ* and the drip well established. Under these conditions the end-result is definite and distinct and there is little or no difficulty in noting the maximum appearance of the dye.

3. In normal individuals the appearance of the excretion as measured day by day is extremely constant, the average being, according to our experience, in 13.7 minutes. A delay of more than twenty-three minutes in the excretion of the dye indicates the presence of some hepatic disease or mechanical obstruction at some point between the biliary ducts and the ampulla of Vater. The most marked delay occurred in biliary cirrhosis; in obstruction the delay varied from day to day when the obstruction was due to stone.

4. The test has proven useful as a means of checking up the technic of non-surgical biliary drainage. It is also of value in the diagnosis of cirrhosis and carcinoma of the liver and obstruction of the common duct from stone or tumor.

The manner in which the tetrachlorphthalein flows may aid in differentiating cases in which there is delay, especially between cholelithiasis, cancer and cirrhosis of the liver and external causes of obstruction. The flow in cases of calculus is usually intermittent and presents a greater variation from day to day, whereas in cirrhosis and other forms of obstruction the flow after once beginning is constant and there is but an extremely slight daily variation.

5. Finally, from these observations, it is evident that the tetrachlorphthalein test is of considerable value as a means of determining liver function, and when properly performed may be of great aid in diagnosis.

NOTE.—The phenoltetrachlorphthalein ampoules in stable form used in the performance of these tests were furnished us by Messrs. Hynson, Westcott and Dunning, of Baltimore, to whom we desire to acknowledge our thanks, and from whom this preparation can now be obtained.

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INSULIN IN THE TREATMENT OF SEVERE DIABETES

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(BY INVITATION)

During the first twenty-four hours the patients remain on the same diet as previous to their admission to hospital, in order to ascertain some idea of the severity of the disease. They are then placed upon a basal requirement diet, which is estimated from the Du Bois chart and the Aub, Du Bois table. Relative food values of the diet are calculated by the use of the Woodyatt (or a slightly modified) ratio. The patients remain on this basal requirement diet for a week, during which time a careful history is taken and complete physical examination done. Blood sugars are estimated before breakfast and three hours after, in order to determine accurately the fasting level and the result of food. The twenty-four-hour specimen of urine is examined qualitatively and quantitatively for sugar and acetone. Patients on a basal requirement diet, the carbohydrate value of which is low, soon excrete fairly constant amounts of sugar. If while on this basal requirement diet the patient becomes sugar-free the diet is raised, and if he is able to take 500 calories over and above his basal requirement the case is not considered sufficiently severe for insulin treatment at the present time. A case of diabetes mellitus is therefore considered severe when unable to metabolize 500 calories over and above his basal requirements.

Before commencing insulin treatment it is essential to know the tolerance of the patient, or, in other words, the number of units of insulin capable of being produced in the patient's own pancreas, since insulin treatment consists in the artificial administration of insulin in sufficient quantities to compensate for the deficiency of the patient's production. The ideal of treatment is, therefore, to

balance the increased diet over and above the patient's own tolerance with the artificial supply of internal secretion.

A unit of insulin is the amount of active principle required to reduce the blood sugar of a rabbit, which has been starved eighteen hours, from its normal level of approximately 0.120 per cent to 0.045 per cent. Although there is at present a slight variation in the strength of the unit, the carbohydrate equivalent in a moderately severe diabetic is about 2.5 grams, or, in other words, one unit of insulin causes about 2.5 grams of glucose to be burned in the moderately severe diabetic. In milder cases the utilization per unit is more than this amount, while in cases complicated by infection with an elevation of temperature the utilization per unit is less.

The dose of insulin is calculated on the height of blood sugar and the average number of grams excreted daily. A patient with a high blood sugar requires a larger initial dose because the blood sugar must be reduced to its normal level.

Insulin is most advantageously given twenty minutes to a half-hour before meals. In this way absorption of insulin and of carbohydrate from the gastro-intestinal tract are taking place at the same time, and the curve of hyperglycemia produced by the absorption of food is superimposed upon the curve of hypoglycemia produced by insulin in such a manner that the patient's blood sugar remains constantly below the kidney threshold. Normally when food is absorbed from the gastro-intestinal tract there is an increase in the production of insulin by the islet cells to deal with the carbohydrate. This is shown by the fact that when a normal dog is given 2 grams of glucose per kilo of body weight, intravenously, the blood sugar immediately rises to 0.400 or 0.500 per cent and rapidly falls to normal within one and a half hours; whereas if the same amount of glucose is given immediately after pancreatectomy the blood sugar falls slightly within the first half-hour, but remains at a high level (0.280 to 0.300), since there are no islets present in the animal to produce insulin. Therefore, one may conclude that the carbohydrate of a meal stimulates the islet cells of the pancreas to produce insulin. Hence there is greater activity of the islets following a meal. By the proper balance (in regard to time and dose) of artificial administration of internal secretion on the one hand and carbohydrate over and above the patient's own tolerance on the other

hand, it is possible to maintain even a severe and long-standing diabetic sugar-free on a diet sufficient for his daily requirements.

There is slight individual variation in the rate of absorption of insulin, and it is sometimes difficult, when a severe diabetic is given a large diet and a large dosage of insulin, to maintain constant normal blood sugar. Usually the patient receives two doses per day, one before breakfast and the other dose before the evening meal. It is sometimes advisable to give a larger dose in the morning, as, for example, a patient may receive fifteen units before breakfast and ten units before supper. Some severe patients require three of four doses per day, whereas milder cases progress favorably on one morning dose.

It has been found advisable to render all cases of diabetes sugar-free on an adequate diet with insulin. The patients are first rendered sugar-free on their basal requirement diet, then diet and dosage of insulin are increased coincidently until the required diet is reached. If small amounts of sugar appear in the twenty-four-hour specimen of urine, each specimen is examined separately in order to ascertain the time of day the excretion occurred. An increase in the dose of insulin previous to the time of excretion will usually abolish the glycosuria. Whether or not glycosuria is injurious to the diabetic is not definitely known at the present time. Patients may progress favorably, feel stronger and gain in weight while excreting small quantities, but it is more normal to maintain the patient sugar-free by the careful balance of insulin and diet. This is difficult in some cases on high diet and in children, because in these cases there is but a narrow margin between hypoglycemic reactions and hyperglycemia. In old, long-standing diabetics where the kidney threshold has been elevated the margin of safety is wider and the cases are more easily controlled.

Insulin shock or hypoglycemic reaction is a definite clinical entity, caused by the overdose of insulin reducing the blood sugar below its normal level. It is always recognizable by the patient, as the subjective sensations are pathognomonic. The reactions depend not only on the extent, but also on the rapidity of fall in the percentage of sugar in the blood. Reactions are characterized by pallor, sweating, stupor, increased pulse-rate, peculiar sensations of impending danger, incoherence in speech, tremulousness and finally coma

and convulsions. Elevation of blood sugar immediately relieves the condition. This is accomplished by the oral administration of glucose if the patient is conscious, or the administration of 10 to 15 minims of epinephrin followed by glucose if the patient is in coma.

Cases of severe diabetes complicated with persistent diarrhea do not respond well to insulin treatment. In these cases there appears to be a hypersensitiveness to insulin, as evidenced by frequent and severe hypoglycemic reactions. In one case of this type where achlorhydria was present the administration of hydrochloric acid and calcium chloride favorably influenced both diarrhea and hypoglycemic reactions.

In cases of long duration in which there has been persistent strain on the islet cells from high blood sugar, when this strain is relieved by adequate dosage of insulin there is an increase in tolerance, as evidenced by the necessity for a smaller dosage. However, in long-standing severe cases of diabetes mellitus, maintained sugar-free on low diets even at the expense of strength and weight, the improvement in the inherent ability of the patient's own islet cells is slower and less marked if present.

Insulin enables the severe diabetic to burn carbohydrate, as shown by the rise in the respiratory quotient following the administration of glucose and insulin. It permits glucose to be stored as glycogen in the liver for future use. The burning of carbohydrate enables the complete oxidation of fats, and acidosis disappears. The normality of blood sugar relieves the depressing thirst, and consequently there is a diminished intake and output of fluid. Since the tissue cells are properly nourished by the increased diet, there is no longer the constant calling for food, hence hunger pain of the severe diabetic is replaced by normal appetite. On the increased caloric intake the patients gain rapidly in strength and weight. With the relief of the symptoms of their disease and with the increased strength and vigor resulting from the increased diet the pessimistic melancholy diabetic becomes optimistic and cheerful.

Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrate so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.

THE ROUTINE TREATMENT OF DIABETES WITH INSULIN

By ELLIOTT P. JOSLIN, M.D.
BOSTON

Successful treatment of diabetes with insulin depends on the utilization of all those measures that have proved of the greatest value in the treatment of diabetes without insulin. These are: adherence to a diet which will keep the urine sugar-free; avoidance of overnutrition or extreme undernutrition, and a method of life compatible with the strength such a diet affords. A knowledge of the fundamental principles of the diet and of the food values of a few foods is essential, otherwise the insulin will be squandered and the patient placed in jeopardy.

Insulin does not cure diabetes. Insulin does not allow a diabetic to eat anything he desires. It is cruel for prominent individuals to make such statements and arouse false hopes. It is true that heretofore there has never been anything discovered as valuable for the diabetic as insulin, but diabetes, though subdued, is not yet conquered.

Insulin is no more dangerous than morphine, and it has these advantages: Whereas an excess of morphine leads directly to sleep, coma and death, an overdose of insulin causes a warning train of symptoms, beginning with nervousness and extreme hunger as the blood-sugar drops below 0.07 per cent; progressing to sweating and tremor, subconscious or evident, and ending with unconsciousness, as the blood-sugar reaches 0.03 per cent, and death is possible. Again, unlike the course in morphine poisoning, recovery follows the simplest of measures—the juice of an orange or from 1 to 3 teaspoonfuls of sugar—and takes place promptly within five to ten minutes. Recovery may be further expedited by 1 cc (15 minims)

of a 1 to 1000 solution of epinephrin subcutaneously administered, though this also is to be followed by the orange or sugar.

It is a mercy that at present insulin becomes inert when given by mouth, and that its use is restricted to a syringe. The medical profession cannot be too grateful to the Insulin Committee of Toronto for limiting the supply and the distribution for a few months. Consider for a moment what would happen if morphine was the drug discovered and then was at once sold over the counter. The useless pancreatic preparations of the past required no supervision; insulin does, because it is potent.

Insulin, nevertheless, should be and can be used by the general practitioner. This I have proved, because already 127 patients have been sent home from the hospital or boarding house across the street and are taking insulin under the supervision of their own physicians. There is no reason why any physician should not treat other patients, provided he spends one hour learning the diabetic diet or makes certain that the patient knows it. This knowledge of diabetic arithmetic is a pivotal point in order to balance diet with drug with enough accuracy to justify the trouble of the treatment. If the diet much overbalances the drug there will be free glycosuria, and the expense and pains are practically wasted. If the drug overbalances the diet there is likely to be a reaction, always fraught with alarm; and, finally, if the physician does not know the diet, he may lose the confidence of his patient.

For example: Five weeks of dietetic treatment failed to control the severe diabetes of Alice S., last summer. With insulin she improved, and when it was time to go home, not her parents, but her old, overworked, country physician traveled nearly two hundred miles to get her, to see for himself how she and other patients were treated, to observe for himself what they ate, and to hear them recite their lessons on food and insulin and sugar tests. Alice learned the diet for the doctor, and Dr. B. learned about insulin for Alice. The partnership has already earned a 40 per cent dividend in weight for the child, and I fancy far more than that in joy for that faithful practitioner.

Intelligent patients can be taught the use of the diet and insulin in a week, and in two weeks the average patient can become free

of acid and sugar, learn what is requisite either in hospital or boarding house or with a diabetically trained nurse in his own home. Thus, with education they accomplish with 5 units what would otherwise require 10 units. Blood-sugar tests are very desirable, but I doubt whether one in ten of my patients has such a test once a month in his own home. The cost of one such test would probably supply them with insulin for a week, and they prefer the insulin. Instead of blood-sugar tests, they depend on frequent Benedict tests of each single specimen of urine, of which the cost of one test is one cent. By testing the urine before and after meals they learn whether the relation between carbohydrate and insulin should be changed. If glycosuria is present and yet the patient is receiving sufficient calories, carbohydrate is reduced until all specimens throughout the day are sugar-free; or if the carbohydrate is below 30 gm. in the diet, insulin may be increased. After a few weeks of preliminary treatment "single specimen" days are only occasionally necessary, and the patient is safe with a test of all that portion of the twenty-four-hour quantity of the urine that is voided at home.

The first diet given a diabetic patient showing glycosuria should approximate that which he has been taking, with these modifications: The calories should be reduced by a marked restriction in fat, and the protein limited to 1 gm. or less per kilogram of body weight; and it is desirable to begin with about 200 gm. of carbohydrate or as much below that quantity as was in the patient's former diet, or, if that is unknown, with an equivalent of the grams of sugar in the urine. For use in the hospital, test and maintenance diets are useful, but advances in dietetic treatment and insulin force their constant modification, so that the one here shown must be regarded as tentative. It is a great advantage not to have invented a formula for computing diets, because one feels quite free to take the best of all systems. Having started the diet, one proceeds each day to the next diet in sequence until the urine is sugar-free. Fasting is practically never necessary for even one meal, since generally the patient becomes sugar-free on Test Diet 3 or 4. Then one skips to that maintenance diet which has about the same quantity of carbohydrate and advances each day. If sugar returns,

TABLE I.—INSULIN DIABETIC DIETS

	Diet.	Total diet.				Carbohydrate (C).						Protein and fat (PF).					Diet.
		Carbohydrate.	Protein.	Fat.	Calories.	5% vegetables.	Orange.	Oatmeal.	Shredded wheat.	Uneeda.	Potato.	Egg.	Cream 20% fat.	Bacon.	Butter.	Meat.	
Test	T. D. 1	181	46	44	1304	300	300	..	3	4	240	3	120	..	..	...	1
	T. D. 2	101	35	43	931	300	300	..	1	2	120	3	120	..	..	...	2
	T. D. 3	66	24	37	693	300	300	..	½	2	...	2	120	..	..	...	3
	T. D. 4	34	15	30	466	300	200	..	..	..	...	1	120	..	..	...	4
Maintenance	C 1+PF1	14	15	30	386	300	...	..	..	..	...	1	120	..	..	...	1
	C 2+PF2	22	19	37	497	300	100	..	..	..	...	2	60	..	15	...	2
	C 3+PF3	32	24	37	557	600	100	..	..	..	...	2	60	..	15	...	3
	C 4+PF4	42	29	52	752	600	200	..	..	..	...	2	60	30	15	...	4
	C 5+PF5	52	32	66	930	600	200	15	..	..	...	2	60	30	30	...	5
	C 6+PF6	64	44	83	1179	600	200	30	..	..	...	2	120	30	30	30	6
	C 7+PF7	74	52	88	1296	600	300	30	..	..	...	2	120	30	30	60	7
	C 8+PF8	84	61	94	1426	600	300	30	..	2	...	2	120	30	30	90	8
	C 9+PF9	98	65	106	1606	600	300	30	½	2	...	2	180	30	30	90	9
	C10+PF10	109	66	119	1771	600	300	30	1	2	...	2	180	30	45	90	10
	C11+PF11	135	80	135	2075	600	300	30	1	2	120	2	240	30	45	120	11
	C12+PF12	159	84	135	2187	600	300	30	1	2	240	2	240	30	45	120	12

for instance, on the carbohydrate and protein and fat for the sixth day (C6+PF6) and the patient is not receiving enough calories, one lowers the diet to C5 or C4 and advances the protein and fat (PF) to PF7 or PF8 or more as needed, or even adds extra fat in the form of cream or butter.

The first dose of insulin should be 1 unit. This is the amount necessary to lower the blood sugar of a 1 kg. rabbit, fasting twenty hours, to 0.045 per cent. It is safer to begin with one unit, because I have known this to bring down the blood-sugar of a diabetic patient with a tolerance for and while taking 91 gm. of carbohydrate to 0.03 per cent. Insulin is more often given than withheld at the hospital as soon as the diagnosis is definitely made, in order to meet the patient's wish to curtail hospital stay. Before the second meal 2 units are given, 3 before the third and so on up to 5 units, and then this quantity is given three times a day and increased or decreased as indicated. Sometimes the extract proves to be unnecessary after a couple of days. During this period the diet also is being changed. Once the patient is sugar-free the attempt is made to get rid of the noon dose by shifting the carbohydrate, as far as is feasible, to breakfast and supper and decreasing the noon insulin by a unit each day. If unsparable the omitted insulin is taken up again, but this time is divided between the doses before breakfast and supper.

The time at which insulin is given varies from one-quarter hour to one and one-half hours before meals, depending on the rapidity of absorption of carbohydrate from the stomach and insulin from the subcutaneous tissue, as estimated after observation of each individual patient.

The place at which insulin is given is most frequently the arm, then the thigh and lastly the buttock.

The average dose of insulin daily for 127 of my patients is 11 units. No patient is now taking in twenty-four hours more than 45 units, but three are taking as many as 30 units, while a considerable number (eighteen) receive less than 5 units a day.

The first of my patients chosen to receive insulin was selected because I knew of none more severe or more strictly faithful to every detail of treatment in the past:

Miss M., aged forty-two years, who had had diabetes for five years, and whose weight had fallen from 157 to 72 pounds (from 72 to 33 kg.); who could scarcely be kept sugar-free on any diet, and who had been down to the street but once in nine months, began insulin August 7, 1922. Since that date she has gained 20 pounds (9 kg.), has a normal blood-sugar before and after breakfast and is sugar-free while taking 10 units daily instead of the 35 units daily which she at one time required. Her diet has been carbohydrate, 25 gm.; protein, 43 gm.; fat, 105 gm.; and I have now raised it to carbohydrate, 30 gm.; protein, 50 gm.; and fat, 110 gm. I am content to have had the weight of my severest case of diabetes increase in eight months by 28 per cent and to have reduced the dosage of insulin from 35 units to 10 units. With the extra food allowed she requires at least 5 units more of insulin. Her weight has again increased to 96 pounds (43.5 kg.). With the restricted diet will she not again be able to reduce her insulin when her further gain in weight makes her once more underfed?

Patients omitting insulin through lack of supply must go to bed and restrict the diet one-third:

Thomas D., my faithful little patient, went home and, unfortunately, in the absence of his home physician, thought he could get along without insulin. After five days he became ill, an intercurrent respiratory infection occurred, coma developed and he returned to the hospital to die in seven hours, October 20, 1922. No other patient with coma has died at the New England Deaconess' Hospital since August 7, 1922.

The treatment of coma with insulin is spectacular; but coma is a diabetic accident, and, like all accidents, to be avoided. At the New England Deaconess' Hospital the lack of coma is to be attributed partly to the training given patients. They are taught, whenever ill from any cause to, (1) go to bed; (2) keep warm; (3) take a glass of hot water, tea, broth, orange juice or oatmeal water gruel every hour; (4) empty the bowels with an enema, and (5) call a physician, who, if he finds acidosis, probably will give them insulin, digitalis and caffein, and may wash out their stomachs. This freedom from coma is perhaps still more to be attributed to the large general hospitals in Boston receiving such emergency cases. With the expansion of the Deaconess' Hospital to 180 beds more of these patients may enter.

In coma, insulin, from published reports, is best given in 10-unit doses every hour for about two to four doses and then every other

TABLE II.—FOODS ARRANGED ACCORDING TO CARBOHYDRATE CONTENT

5%		10%[1]	15%	20%
1 to 3%	3 to 5%			
VEGETABLES (Fresh or Canned)				
Lettuce	Tomatoes	String beans	Green peas	Potatoes
Cucumbers	Brussels sprouts	Pumpkin	Artichokes	Shell beans
Spinach	Water cress	Turnips	Parsnip	Baked beans
Asparagus	Sea kale	Kohlrabi	Canned lima beans	Green corn
Rhubarb	Okra	Squash		Boiled rice
Endive	Cauliflower	Beets		Boiled macaroni
Marrow	Egg plant	Carrots		
Sorrel	Cabbage	Onions		
Sauerkraut	Radishes	Green peas, canned		
Beet greens	Leeks			
Dandelion greens	String beans, canned			
Swiss chard	Broccoli			
Celery	Artichokes, canned			
Mushrooms				
FRUITS:				
Ripe olive (20 per cent fat)		Watermelon	Raspberries	Plums
Grape fruit		Strawberries	Currants	Bananas
		Lemons	Apricots	Prunes
		Cranberries	Pears	
		Peaches	Apples	
		Pineapple	Huckleberries	
		Blackberries	Blueberries	
		Gooseberries	Cherries	
		Oranges		

	30 gm., 1 oz., contain approximately			
	Carbohydrates. Gm.	Protein. Gm.	Fat. Gm.	Calories.
Oatmeal (dry weight)	20.0	5.0	2	118
Shredded wheat	23.0	3.0	0	104
Uneeda biscuits (two)	10.0	1.0	1	53
Cream (40 per cent)	1.0	1.0	12	116
Cream (20 per cent)	1.0	1.0	6	62
Milk	1.5	1.0	1	19
Brazil nuts	2.0	5.0	20	208
Oysters (six)	4.0	6.0	1	49
Meat (cooked, lean)	0.0	8.0	5	77
Chicken (cooked, lean)	0.0	8.0	3	59
Bacon	0.0	5.0	15	155
Cheese	0.0	8.0	11	131
Egg, one	0.0	6.0	6	78
Vegetables (5 per cent group)	1.0	0.5	0	6
Vegetables (10 per cent group)	2.0	0.5	0	10
Potato	6.0	1.0	0	28
Bread	18.0	3.0	0	84
Butter	0.0	0.0	25	225
Oil	0.0	0.0	30	270
Fish: cod, haddock (cooked)	0.0	6.0	0	24
Broth	0.0	0.7	0	3

[1] Reckon average carbohydrate in 5 per cent vegetables as 3 per cent; of 10 per cent vegetables as 6 per cent.

hour for four doses more, if necessary, One should be very cautious before giving more than 60 units in twelve hours. Few cases have required more than 100 units. The blood-sugar percentage and the urine sugar, in addition to the clinical state of the patient, are the best guides in treatment. In some case it may be safer to give 5 or 10 gm. of carbohydrate by mouth to offset the insulin, and some of the most successfully treated patients have received a few grams, from 15 to 30, of sodium bicarbonate. Promptness in beginning treatment is everything.

Insulin can be discontinued in a small fraction of cases. Those patients may be able to omit it who receive it temporarily because of an exacerbation caused by complications, and some patients whose diabetes is of recent onset, though perhaps the latter should

TABLE III.—RESULTS OF TREATMENT. SUMMARY OF 127 PATIENTS WITH DIABETES TREATED WITH INSULIN AND DISCHARGED TO THEIR HOME PHYSICIANS

No. of cases.	Age at onset, years.		Duration of disease, years.		Treatment with insulin.		Gain in weight.	
	Aver.	Range.	Aver.	Range.	Duration, days.	Units daily aver.	Lbs.	%
127	29	1–65	4	0.3–20	107	11	4	5
INSULIN IN THE TREATMENT OF DIABETES IN CHILDREN FIFTEEN YEARS OF AGE OR UNDER								
31	7	1–15	2	0.3–8	122	10	5	11
PATIENTS TAKING 6 OR LESS UNITS DAILY (CHILDREN UNDER FIFTEEN)								
13	6	1–13	2	0.3–4	89	4	3	8

receive it intermittently as a prophylactic against increasing severity. Many such instances in children are under observation.

To the Insulin Committee of Toronto, and through its recommendation to the Eli Lilly Company as well, I have been indebted for the rare privilege of using insulin. For this I cannot be grateful enough. The contribution of Banting and Best to the treatment of diabetes is greater than I ever expected to witness.

THE TREATMENT OF DIABETIC COMA WITH INSULIN

By NELLIS B. FOSTER, M.D.
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Until the last year it has not been my good fortune to see a recovery from diabetic coma. There are reports in the literature, it is true, that recovery has taken place, but with possibly one or two exceptions coma quite promptly recurred and led to death. Since October, 1922, 15 cases of diabetic coma have been treated; of these 8 recovered from the coma and of these 8 who recovered 5 are still alive. These cases were treated with insulin. Having a means of controlling the primary, acidosis factor in coma, we have been able also to study secondary, contributory factors and devise means to combat them. There seem to be three abnormal conditions which are notable in all cases of diabetic coma: Acidosis, desiccation of the tissues and myocardial weakness. While acidosis is primary and in a sense probably initiates other disorders in the body-chemistry, it is also true that death may result from one or both of the secondary factors after the acidosis has been corrected. Some years ago, when the causation of diabetic coma was still uncertain, Magnus-Levy asserted that the theory of death from acidosis must be accepted unless treatment with alkalies had been successful to the degree of rendering the urine alkaline. We no longer measure degrees of acidosis by urine examinations, but death may occur in diabetic coma after the blood no longer gives evidence of acidosis, and there are now several reports of death in diabetic coma after the urine had become alkaline. I have seen one such case. Therefore, I wish to emphasize that other factors than acidosis demand attention in the treatment of diabetic coma, and that they cannot be neglected.

Everyone who has seen cases of diabetic coma must have been impressed by the evidence of desiccation of the tissues. Although

there may be no fever, the mouth and pharynx are invariably dry and parched to a degree usually seen only in febrile disease. The reduced intraocular tension is also probably an effect from water loss. As a matter of fact, every case of severe diabetes presents evidence of the difficulty of maintaining the water balance in the body. Now, as acidosis becomes more and more severe, two conditions develop which prevent the patient from drinking adequate amounts of fluid: He is often nauseated, sometimes he vomits, and although the thirst be agonizing, he fears to drink or vomits when he does drink. In the course of hours he becomes drowsy and drinks less and less as stupor creeps on him. In brief, less water is taken into the body as acidosis progressed. But during this period the water elimination does not decrease. The glucose excretion is extreme and persistent and constantly abstracts water from the tissues for urine formation. Pulmonary ventilation is increased and augments the water loss of the expired air. Even the small amount of endogenous water is diminished, since both carbohydrate and fat, which normally are burned to carbon dioxide and water, now are not oxidized (glucose) or are oxidized only to intermediate ketone bodies. A moment's thought on these abnormal conditions clarifies the extreme desiccation which is notable in cases of diabetic coma. The significance of desiccation alone as a cause for abnormal metabolic states was demonstrated in the classical experiments of Woodyatt.

It has been recognized for years that when fluids are injected intravenously in cases of diabetic coma special care must be exercised or death may suddenly occur. The fluid must be given more slowly than is necessary in other diseases and the amount injected at one time must be small. It is a general belief, I think, that the myocardium in diabetic acidosis is seriously damaged and must be protected. The hearts of young subjects examined at autopsy show hypertrophy and cloudy swelling of the muscle. During life there is usually tachycarida and occasionally delirium cordis. On one occasion it happened that a patient came out of coma and conversed about his disease and then developed symptoms which seemed typical of acute cardiac failure, and died. There is nothing definite and little is known of the vascular mechanism in severe acidosis.

But until we possess a better understanding it seems wise to use the general measures employed when a similar train of signs are presented.

There is no means of determining in an individual case the amount of insulin which will be required to stop the formation of ketone bodies. The smallest amount effective in my series was 70 units, given in a period of six hours, and the largest dosage used in a case that recovered was 180 units during twelve hours. In the beginning our dosage was too small, because we had to economize in insulin. Now we are more liberal. In such a critical condition the best rule is to be sure that one uses enough. The first dose may be 25 units at least in adults and repeated smaller doses at intervals of an hour or two. The urine should be tested for sugar every two or three hours, and heavy dosage is advisable so long as large amounts of sugar are excreted. When the sugar in the urine begins to fall then the dosage of insulin can be decreased and the interval between doses lengthened. It is evident, from numerous observations, both in coma and in severe acidosis, that the blood sugar is most variable and apparently has no clear relation to the clinical symptoms. The concentration may be as low as 250 mg. per cent, a not uncommon figure in many cases in good condition and free from ketonuria. Then too it has been observed that the blood sugar may be higher after the patient has recovered from coma than it was during coma. This is probably due to the glucose given in the rectal instillations.

That adequate amounts of glucose be available in the tissues seems to me important. Acidosis is initiated by failure of the oxidation of glucose. Progressively, then, fat and protein are substituted as sources of energy. The glucose from protein not being utilized the metabolism of fat is progressively imperfect. The primary object in treatment is to substitute a carbohydrate metabolism for a dominant fat metabolism. Insulin makes it possible to accomplish this end, but only when glucose is available for oxidation after insulin is given. Therefore it is logical, in our opinion, to use glucose in clysters and in beverages. For the latter orange juice is satisfactory and gratefully taken.[1]

[1] For rectal instillation Karo syrup is an available source of glucose. Two ounces to the pint of water makes a solution of approximately 5 per cent strength. Only pure dextrose may be used intravenously.

The use of alkalies in severe acidosis has been a debated subject. On purely theoretical grounds there is ample basis for the administration of large doses of bicarbonate of soda. Underhill's experiments, some years ago, suggested that more sugar was utilized when alkalies were administered, and Mosenthal has recently applied this principle to human subjects. During coma little liquid can be given by mouth and the mount of alkaline salts which can be given intravenously is insignificant. We have used 3 per cent bicarbonate of soda solution along with glucose for rectal instillations and by the Murphy drip method. Any good effect of the alkali, *per se*, is obscured because of several measures employed simultaneously. Physiological saline solution has been used for hypodermic and intraperitoneal injections and 3 per cent sodium bicarbonate solution intravenously.

The variation in procedures in different cases is shown in the summaries or clinical records. The direct aims in our methods have been to arrest ketone formation by restoring an adequate oxidation of glucose; to relieve desiccation by introducing water into the body through every avenue of absorption; and finally, to support or stimulate the circulation by digitalis and caffein.

REPORTS OF CASES

Y. F., aged forty-eight years, was admitted to the Private Patient's Building, October 4, 1922. She had had diabetes five years and a week before developed infection of her ring finger following the prick of a pin. Operation was performed October 4, 1922 (Dr. Hitzrot) and her left ring finger was amputated with removal of the metacarpal bone; the flexor tendons were gangrenous and the wound was left open. Culture showed Staphylococcus aureus. October 7 the urine contained 2.7 per cent of sugar and was strongly positive for acetone. The blood sugar was 0.364 per cent. The patient was in profound coma. Murphy drip was started and 30 cc of iletin given during the next six hours. She died at 6 P.M. This patient was a mild diabetic, her disease was temporarily severe and acidosis was initiated by infection. Had we had sufficient iletin we believe her life could have been saved.

C. H., aged sixteen years, had been a patient in the Methodist Episcopal Hospital in Brooklyn for a month before transfer to the New York Hospital. He was admitted in coma, October 3, 1922. Prior to transfer he had

received 30 units of iletin. The typical signs of diabetic acidosis were present. The blood CO_2 was 9.9 volume per cent and the sugar 260 mg. During the first twelve hours this patient received 100 units of iletin and another 100 units during the following eighteen hours. Fluids were given by rectum at first and as soon as the patient roused sufficiently by mouth also. The patient became conscious and rational about fourteen hours after treatment commenced. His food at first was 1 liter of milk per day with orange juice, later a measured diet. Recovery was perfect and he was discharged in November. He was faithful in executing directions and gained 10 pounds in weight on continued iletin treatment of 15 to 20 units per day. In February he contracted influenza and died, whether in coma or not we do not know.

A. D., a woman, aged forty-seven years, had had diabetes for an indefinite period. On account of diabetic gangrene her left leg had been amputated just below the knee. Sugar had been eliminated from the urine before operation. The operation was followed by a febrile reaction and sugar reappeared in the urine. December 26, 1922, two days after the operation, the patient was stuporous and had a temperature of 101° F.; her blood sugar was 0.3 per cent; urinary sugar approximately 2 per cent, and acetone was present. By the use of 50 units of iletin in the next twenty-four hours urinary sugar was reduced to a trace and the blood sugar reduced to 0.17 per cent. The blood CO_2 was raised from 20 to 40 per cent. On the appearance of gas bacillus infection in the wound iletin treatment was abandoned.

J. C., aged twenty-one years. This patient gave a six-day history of extreme polydypsia and polyuria. Thirty-six hours previous to admission he felt very weak and faint. Twelve hours previous to admission he seemed to be somewhat delirious and six hours later he became comatose and remained so until he was brought to the hospital. Examination of the urine by his doctor had shown sugar of 4 per cent but no acetone or diacetic acid. No albumin or casts were present. The patient was told he had diabetes and was referred to the hospital. Past history revealed that he had gained weight from 140 pounds to 230 pounds, his present weight, in the course of the last three years. His father and mother were both rather obese, but not particularly large.

Physical examination showed a very obese young man, with flushed skin in deep coma. His respirations were 55 per minute and the pulse-rate 120. There was suggestive acetone odor on his breath. The heart sounds were very distant and the second sound was scarcely audible. His blood-pressure was 86/56. Examination of the eye-grounds disclosed nothing abnormal. A diagnosis of diabetic coma was made and the patient was

treated with iletin injections and Murphy drip of 2 per cent glucose and 2 per cent sodium bicarbonate. As the heart was evidently failing he was given 4 ampoules of digifolin subcutaneously. The patient did not recover consciousness but died after eight hours, having developed edema of the lungs. Immediately after death the bladder was catheterized but only 25 cc of urine was obtained. *This showed sugar and a faint trace of acetone.* Nothing abnormal was found in the postmortem examination. Blood taken four hours after death had a sugar content of 1.058 per cent. Non-hemolytic streptococci were grown from the blood culture.

Mrs. N. S., aged twenty-eight years, developed diabetic coma December 9. She had had diabetes about a year and had failed in health rapidly. Her treatment in the past seemed to have been rather indefinite. On December 8 and 9 she had felt sick and her bowels had not moved for several days. The patient was emaciated, weighing 85 pounds. The face was flushed and the respirations were characteristic of acidosis. She was not in deep coma but could be roused, not however sufficiently to answer questions. The blood sugar was 450 mg. per cent and the CO_2, 13 volume per cent. The routine method of treatment was used and 5 units of iletin were given every two hours. As soon as the patient was sufficiently conscious, a matter of six hours, she received milk and orange juice. On December 13 the total glucose tolerance was determined to be 60 grams (including glucose, from protein, determined on the basis of urinary nitrogen). A diet containing 1000 calories was ordered and with 10 units of iletin daily the patient maintained a sugar-free urine and was sent home December 22, weighing 89 pounds.

S. B., aged thirty-six years, was transferred from Bellevue Hospital to New York Hospital, January 1, 1923. The patient was unable to speak any language familiar to the staff and the only history was of severe diabetes recognized at Bellevue. He was admitted in deep coma, although he had had 50 units of iletin during the six hours before his transfer. The usual routine treatment was carried out and 5 units of iletin were given every two hours. The patient recovered from coma in about ten hours. As soon as consciousness returned the patient vomited, and this continued at short intervals. Examination revealed signs suggesting acute dilatation of the stomach. This was treated by gastric lavage and no fluids were given by mouth. In spite of this obstacle the patient continued to improve and the urine was free of sugar on the fourth day. He left the hospital against advice, but has only recently returned to Bellevue for treatment (April).

D. G., aged fifty-one years, had had diabetes of a mild type for a number of years. In the latter part of December he took cold, which resulted in

bronchitis and then pneumonia. He became stuporous during the day of January 2 and was in coma when seen January 3. Samples of blood were not secured at the first examination. He was given 5 units of iletin every three hours. Consciousness returned in ten hours and the blood sugar was then 0.306 per cent and the CO_2, 32 volume per cent. The iletin dosage was decreased and everything progressed favorably for a week. We then ran out of iletin and this patient had none for five days. His diet at the time iletin was discontinued contained 1400 calories. It was reduced to 770 calories (protein, 40; carbohydrate, 40; fat, 50). The blood sugar was then 0.174 per cent. On the sixth day coma developed a second time, and having received a new stock of iletin, 25 units were given in one dose and 10 units every two hours. Consciousness returned completely after about twelve hours. The patient died January 23 of pulmonary abscess.

M. L., aged six years, was admitted February 6, 1923. History of diabetes of three years' duration. Child became drowsy about twenty-four hours before admission to the hospital. The temperature was 99.8° F., pulse 135, respirations 40. The patient was drowsy and the tongue and pharynx were dry. The reflexes were present but sluggish. She was able to swallow, and orange juice and water were given. Glucose in a 5 per cent solution was administered by Murphy drip and 200 cc was absorbed in the first six hours. The first dose of iletin was 25 units and three hours later 10 units; 70 units were given in all in the first fifteen hours. The urine then contained no sugar and the blood sugar was found to be 0.047 per cent. There were no signs of shock but iletin was discontinued temporarily. For the first two days milk alone was given and then a standard diet. This patient is receiving 12 units of iletin per day, which enables her to utilize a diet of 1100 calories. She has gained in weight and her condition is satisfactory.

H. W., male, aged twenty-eight years, was admitted to Private Pavilion February 6, 1923. He was said to have had diabetes two years. For four days he had complained of headache, anorexia, nausea and constipation. On the morning of February 6 he was given a colonic irrigation at eleven o'clock and became stuporous an hour later. At 6 P.M. the temperature was 101° F., pulse, 112; and respirations 32. The patient was deeply comatose with typical respirations, soft eyeballs, immobile pupils and absent reflexes. Treatment consisted of soda bicarbonate solution intravenously and 5 per cent glucose by the Murphy drip method, black coffee by gavage and iletin. During three hours, from 6.30 to 9 P.M., 90 units of iletin were given. Death occurred at 9.15 P.M. The blood taken just after death contained 375 mg. per cent sugar.

Patient M. Z. was admitted to the Second Division, New York Hospital, February 8, 1923, in the morning, in diabetic coma. The urine showed sugar; blood chemistry was not done. She was given an initial dose of 25 units of iletin and following that was given 10 units every three hours. A rectal instillation of sodium bicarbonate and glucose was given every four hours. The patient did not come out of coma and died the night of admission. She had been ill for only six months and there was a rapid increase of symptoms during the last week before admission. During the ten hours in the hospital she received 45 units of iletin. She had been in coma about six hours before admission and the duration of the coma was about fifteen hours. This patient received only 45 units of iletin, probably an inadequate amount.

L. T. This patient had been treated under Banting, in Toronto, in October, 1922. Iletin had been abandoned in January and the patient had eaten freely. He was admitted to Lincoln Hospital in coma February 26, 1923, at 9.30 P.M., and was treated by my assistant, H. F. Spencer. The temperature was normal and pulse 150+. The patient was emaciated and breathing in a typical way; the pupils were small and sluggish and the reflexes absent. Treatment consisted in the routine measures to relieve desiccation and iletin; 70 units were given in the first six hours and the patient became conscious and rational. The blood sugar was 395 mg. per cent on admission and rose to 638 mg. per cent at the end of twenty-four hours. Improvement was continued and the urine was free of ketones on the third day after admission. On a diet of protein, 45; carbohydrate, 52; fat, 65; with 20 units of iletin per day, the sugar disappeared from the urine. Indefinite pulmonary signs led to *x*-ray examination, which suggested a resolving pneumonia. This patient is alive and doing well.

Mrs. E. S., aged fifty-six years, developed diabetic coma February 28, 1923. She had had diabetes some seven years. The disease has caused little inconvenience until about six months ago. Since then there has been a rapid loss in weight and she has become too weak to leave her bed. The diet has been of the usual indefinite type, and according to reports from commercial laboratories the urine had contained 3 to 6 per cent of sugar and also ketone bodies.

The patient was a small, very emaciated woman. Her face was sallow, slightly flushed and the respirations were rapid and deep. She was semi-comatose. The temperature was 96° F., pulse, 100; respirations, 30. The pupils reacted slightly, but other reflexes could not be elicited. The intraocular tension felt decreased. The blood sugar was 535 mg. per cent

and the CO_2 11 volume per cent. Treatment consisted of an enema followed by a 10 per cent glucose and 4 per cent soda bicarbonate instillation by means of the Murphy-drip method. 25 units of iletin were given at once and 10 units every two hours until the urine was free of sugar. This occurred at 8 P.M., March 1. The patient became conscious about fourteen hours after treatment was commenced. March 2 the blood sugar was 136 mg. per cent. From March 1 to 7 the diet consisted of 1 liter of milk and the juice of twelve oranges per day; 60 to 80 units of iletin were given daily in doses of 10 units each. March 7 the diet prescribed was protein, 100; carbohydrate, 150; fat, 210; and this was changed March 13 to protein, 70; carbohydrate, 160; fat, 100. She was now receiving 40 units of iletin per day and sugar disappeared finally from the urine March 17. The patient was sent home March 20, having gained 10 pounds. The blood sugar ranged from 135 to 145 mg. per cent and the urine was free of sugar and ketones. Her present diet is protein, 70; carbohydrate, 100; fat, 160, and 40 units of iletin per day is taken in two doses. Her condition is satisfactory.

The next case was the most difficult of any of those that survived. The acidosis factor appeared to be less pronounced than in some of the other cases, but vomiting and impending cardiac failure were menacing features, and only the tireless vigilance and courageous measures used by Dr. Hauser and Dr. Thompson of our staff saved the patient.

M. B., aged twenty-six years, was admitted to the hospital March 26, 1923. He had had diabetes about two years and had lost about 40 pounds. On the day before admission the patient had cramps in the abdomen, headache and was short of breath. He was excessively thirsty but vomited whatever he drank.

At the time of admission the patient was drowsy. The temperature was 98° F., pulse, 134 and respirations, 42. Hypotension of the eyeball was noted and the reflexes seemed abolished. The appearance of the mouth and pharynx and the feeling of the muscles indicated severe desiccation. Iletin was given at once. The bowel was cleaned and instillations of glucose and soda started. After several attempts to give fluid by mouth, which induced vomiting, the stomach was lavaged and fluid by mouth discontinued. During the first twenty-four hours 900 cc of physiological saline was administered by hypodermoclysis. Small amounts of the saline were given intravenously and were injected into the peritoneal cavity. The pulse was small and rapid and at times cardiac failure was

impending. For this caffein and digitalis were given hypodermically. After the patient had been under treatment about twenty hours there was a sudden collapse. It seemed at the moment that this might be due either to heart failure or to excessive iletin. Glucose was injected into a vein and cardiac stimulants used. The condition gradually improved but not promptly. The iletin dosage had been liberal; 30 units were given on admission at 6 A.M.; 20 units at 7 A.M.; 15 units at 8, 9 and 10 A.M.; and 10 units every two hours thereafter until midnight, when the urine was free of glucose.

The blood taken shortly after the first dose of iletin contained 357 mg. per cent of sugar and the CO_2 was 15.7 volume per cent. Four hours later the sugar was 250 mg. per cent and the CO_2 24 volume per cent. After twenty hours the patient gradually improved and is now in excellent condition, and taking a liberal diet.

D. G., aged thirty-one years, had discovered, as a result of examination for insurance a year ago, that he was diabetic. He had had no symptoms until about three months ago. Two days before I saw the patient he had taken cold and had fever; the following day he was drowsy and feverish, and during the night had some difficulty in breathing. In the morning of February 5 he was semiconscious. When I saw the patient with Dr. Schultheis at noon he was stuporus but could be roused to answer questions. Air-hunger was notable and the intraocular tension was reduced. The urine contained about 6 per cent of sugar and gave strong reactions for ketones. Blood taken at this time contained 0.656 mg. per cent sugar and the CO_2 combining power was 14 volume per cent. The first dose of iletin, 20 units, was given about 1 o'clock, and 10 units more at 3 o'clock. The usual supplementary measures were commenced. At 3 o'clock there seemed definite improvement; the patient roused and discussed his treatment. About 4 o'clock the pulse became very rapid, 140, and later irregular, and the patient seemed in collapse. Cardiac stimulents, including adrenalin, were given without notable result. During the next couple of hours the condition appeared more and more like that of cardiac failure. Dyspnea persisted, but the respirations had lost the typical air-hunger character. Death occurred about 6 o'clock the same day.

The following case presented an unusual clinical picture. The signs in some respects were not those of diabetic coma, but the progress of the disease is most suggestive. It is unfortunate that adequate laboratory data are not available, the critical day of sickness having fallen on a Sunday.

J. F., aged fifty-one years, case of Dr. B. S. Barringer, had had diabetes about twelve years. By using moderate restriction of diet he had maintained good health and had not been restricted in his activities. Early in 1923 he developed symptoms which resulted in his consulting a genito-urinary surgeon. Cystopic examination revealed a malignant papilloma of the bladder, which was treated with radium. Following this treatment there was retention of urine and an excessive irritability of the bladder, necessitating frequent catheterizations; for a period, every two hours, day and night. It seemed desirable to give attention to the diabetes in order to reduce the urine volume primarily and also to improve the patient's condition sufficiently to permit completion of the urological treatment.

At this time the patient seemed to present a problem of no unusual difficulty. He was weak and emaciated, but there was no evidence of significant infection. The temperature, pulse and respirations were normal.

The urine volume averaged about 2 liters and contained 80 to 90 grams of glucose; there was a moderate acetone reaction, but none with ferric chloride. The blood sugar was 250 mg. per cent, which seemed at the time moderate in degree. Nephritis was suspected but no supporting evidence was secured; the urea nitrogen of the blood was 13.8 mg. per cent. The patient was given a diet containing 1800 calories and 75 grams of carbohydrate, and iletin treatment was started with a dose of 45 units per day. He was encouraged to drink as much water as possible.

The following day there had been no abatement of the glycosuria, and since the iletin dosage seemed too large to continue with only a moderate elevation of blood sugar, it was given in 5-unit doses every two hours and each voiding of urine (catheterization) tested for sugar; 50 units were given without detectable effect during the day. The patient seemed very weak and intoxicated, but did not then impress me as suffering from acidosis. The morning of the third day he was definitely worse. He was rather drowsy, the respiratory rate has increased to 40 and the tongue was dry. The patient had no appetite and the diet was discontinued. He was given as much orange juice as he would take and 1 liter of milk. A solution of 5 per cent glucose and 3 per cent soda bicarbonate were injected by the Murphy drip method, at intervals. During this day about 1800 cc of water was given intravenously and subcutaneously. Alkalies were administered in the intravenous solutions and by mouth; 20 units of iletin were given at 10 o'clock and the same dose intravenously at 11 o'clock; 10-unit doses were given every two hours until 9 o'clock in the evening, a total of 110 units during the day. There was no abatement in the intensity of the glycosuria; ketone bodies were still present but the reaction with ferric chloride was faint. The patient was evidently becoming worse rapidly in spite of all that could be done. The pulse was weak, and cardiac failure

being feared, caffein was used intravenously. The same measures were continued until death occurred six hours later. The patient did not develop a typical coma; there was stupor, but until an hour of two before death he could be roused. The respirations were at times forty per minute, but for some hours prior to death were 30. and were not characteristic though suggestive of acidosis. The temperature was normal. In the absence of necessary analyses of the blood I am uncertain whether this patient died of diabetic acidosis or some unrecognized complication. It is the only case I have seen in which iletin treatment produced no definite effect upon the glycosuria.

[We are glad to acknowlege indebtedness to the Eli Lilly Company for supplies of iletin (Insulin, Lilly) which were furnished gratis during the experimental period of its use.]

EXPERIMENTS WITH INSULIN

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As we stand on the threshold of a new epoch of diabetes, it is possible to look back upon the problems of the epoch just closed and forward upon problems of the new epoch that is beginning. Diet regulation is still necessary in connection with insulin treatment, therefore the problems of diet retain their full importance. The various differences of opinion on this subject were not settled during the past epoch of diet treatment. The undernutrition treatment, for example, has been opposed by some persons who believe that fat is harmless in the diabetic diet; others again have regarded protein as especially injurious, through its specific dynamic action or through unknown toxic or irritative effects; and still larger numbers have believed that attention need be paid only to carbohydrate (preformed or from protein or other foods) in the diet or in the metabolism. The brilliant discovery of insulin has furnished a new means of solving these old problems, for having the internal secretion of the pancreas now in our hands it is possible to determine the actual quantitative requirement for it created by one form of diet as compared with some other form of diet.

Second, with reference to the new problem of the physiological rôle of insulin, it is evident that most investigators have viewed it as connected only with carbohydrate metabolism and have sought to establish some quantitative relation between insulin dosage and the sugar in the urine or in the diet or in the metabolism. Such relations seem to be irregular at best, but those who have obtained any results in this direction have done so by maintaining fixed conditions in other respects and varying the quantities of either

carbohydrate or insulin. It may be illuminating to find that equally decisive results are obtainable by keeping carbohydrate and other factors constant and varying only the fat or the total calories in the diet. By giving heed to such experiments, chemists and physiologists may perhaps avoid basing their investigations of the biological rôle of insulin upon false premises.

The planning of such experiments may differ somewhat according to the tests of tolerance which are preferred by different investigators. Some may take the blood-sugar as a guide, others will consider that overtaxed tolerance is shown by the beginning of glycosuria. Others again will depend upon the quantitative differences of sugar excretion produced by different diets in patients having continuous glycosuria. Though this last method, which corresponds to the so-called "carbohydrate balance" of the older writers, is probably the least accurate of all, decisive results can be obtained by any of these methods provided suitable precautions are taken in other respects. One of the most important of these precautions is the duration of the experiments. It has long been known by upholders of the undernutrition principle that the influence of fat, alcohol or other non-carbohydrate foods and of the body weight is generally slow. This influence is manifest most quickly and powerfully when the severest possible cases are chosen and large caloric changes in the diet are made suddenly. The tests shown here today are chiefly of this kind in order that results might be shown within the period of time which can be conveniently represented in lantern slides. When the cases are somewhat milder or the changes in diet less extreme the results are just as constant and positive, provided the patient's assimilative power doses not change meanwhile; but it may be necessary to extend the duration of the experiments to weeks or even months. These experiments are essentially the same as those upon which the undernutrition treatment was based, the sole difference being that it is now possible to express the demands upon the island function quantitatively in terms of units of insulin.

Remarks on Table I. This four-year-old child with severe diabetes was free from glycosuria and hyperglycemia on a diet of 60 gm. protein, 16 gm. carbohydrate and 394 calories, with 2 units of insulin per day.

TABLE I.—CASE NO. 574

Date, 1922.	Diet.				Glycosuria, gm.	Plasma sugar mg. per 100 cc.	Weight, pounds.	Insulin units.
	P. gm.	F. gm.	C. H. gm.	Cal.				
Sept. 9	60	10	16	394	O	....	21	2
10–12	60	10	16	394	O	....	21	2
13	60	10	16	394	O	100	21	2
14–18	60	10	16	394	O	....	..	2
19	60	10	16	394	O	....	22	2
20–23	60	10	16	394	O	126	..	2
24	60	60	6	804	O	....	20	2
25	60	60	6	804	1.7	....	..	2
26	60	60	6	804	3.7	....	20	2
27	60	60	6	804	8.2	....	..	2
28	60	60	6	804	3.6	....	20	2
29	60	60	6	804	5.0	....	..	2
30	60	60	6	804	6.2	....	..	2
Oct. 1	60	60	6	804	8.7	....	21	2
2	60	60	6	804	10.1	....	..	2
3	60	10	11	374	7.1	254	21	2
4	60	10	11	374	5.8	....	..	2
5	60	10	11	374	O	....	21	2
6–13	60	10	11	374	O	....	..	2
14	60	10	11	374	O	159	21	2
15	60	10	11	374	O	....	..	2
16	60	10	11	374	O	....	21	2
17	60	10	11	374	O	....	..	2
18	60	10	11	374	O	....	21	2
19	60	10	11	374	O	100	21	2

September 24. The protein was kept unchanged, the carbohydrate was reduced by 10 gm. and the fat was increased by 50 gm. The glucose value of this diet, according to Woodyatt's rule, was 5 gm. less than before, but the total calories were raised to 804 per day. Glycosuria began with unusual promptness, owing probably to the severity of the case, and increased to as much as 10.1 gm.

October 3. A lower diet with the same glucose value was resumed. With unchanged insulin dosage, glycosuria was absent after October 4 and by October 19 the plasma sugar was again normal.

Remarks on Table II. In this case glycosuria was absent and hyperglycemia steadily diminished on a diet of 60 gm. protein, 25 gm. carbohydrate and 1100 calories, with 6 units of insulin per day.

January 8. The carbohydrate was reduced by 5 gm. and the fat increased by 24 gm., raising the diet to 1300 calories. The rise in plasma sugar became evident on January 12 and was partially controlled by increase of insulin to 8 units daily.

TABLE II.—CASE NO. 85

Date, 1922.	Diet.				Glycosuria, gm.	Plasma, sugar mg. per 100 cc.	Weight, pounds.	Insulin units.
	P. gm.	F. gm.	C. H. gm.	Cal. gm.				
Dec. 17	60	84	25	1100	○	....	103	6
20	60	84	25	1100	○	246	102	6
23	60	84	25	1100	○	192	102	6
27	60	84	25	1100	○	145	103	6
31	60	84	25	1100	○	160	104	6
1923								
Jan. 5	60	84	25	1100	○	139	104	6
8	60	108	20	1300	○	130	104	6
12	60	108	20	1300	○	166	105	6
14	60	108	20	1300	○	....	106	8
17	60	108	20	1300	○	162	106	8
20	60	108	20	1300	○	182	106	8
21	60	186	20	2000	○	192	107	8
24	60	186	20	2000	○	254	....	8
26	60	186	20	2000	○	220	107	8
30	60	186	20	2000	++	395	106	8
Feb. 1	60	186	20	2000	++	....	....	8
2	60	186	20	2000	+	272	104	8
4	60	186	20	2000	○	....	105	12
5	60	186	20	2000	○	294	....	12
8	60	186	20	2000	○	....	107	15
12	60	186	20	2000	○	152	108	15

January 21. The fat was further increased so as to raise the total calories to 2000. Glycosuria and hyperglycemia were evident in the following period up to February 2. On February 2 the sugar excretion was stopped by an increase of insulin to 12 units, but a further increase to 15 units on February 8 was necessary in order to reduce the plasma sugar to 0.152 per cent.

Remarks on Table III. On a carbohydrate-free diet of 75 gm. protein, 5 gm. fat and 345 calories, this weak and emaciated woman was free from glycosuria with 2 units of insulin per day, and the plasma sugar also fell to 0.139 per cent. The addition of 100 gm. fat beginning November 19 produced glycosuria and marked hyperglycemia by November 26.

December 3. A further addition of 50 gm. fat increased the glycosuria, notwithstanding the increase of insulin dosage to 4 units per day.

A change of diet on December 17 reduced the total calories to 600 by withdrawal of fat, while 12 gm. carbohydrate was added to compensate for the supposed glucose value of the fat. With the same insulin dosage of 4 units daily, glycosuria was absent after January 7, and after January 11 the plasma sugar was below 0.2 per cent.

TABLE III.—CASE NO. 54

Date, 1922.	Diet: P. gm.	F. gm.	C. H. gm.	Cal.	Glycosuria, gm.	Urinary nitrogen, gm.	Plasma sugar, mg. per 100 cc.	Weight pounds.	Insulin units.
Nov. 3	75	5	0	345	0	12.41	230	69	2
7	75	5	0	345	0	12.24	159	69	2
9	75	5	0	345	0	11.75	157	..	2
13	75	5	0	345	0	16.97	175	68	2
16	75	5	0	345	0	8.83	139	68	2
19	75	105	0	1245	0	12.92	166	67	2
26	75	105	0	1245	++	10.26	366	67	2
Dec. 1	75	105	0	1245	8.81	8.81	375	69	2
3	75	155	0	1695	13.70	8.68	...	..	2
6	75	155	0	1695	31.32	10.00	341	68	2
7	75	155	0	1695	29.50	10.14	...	..	4
12	75	155	0	1695	35.64	8.29	416	66	4
15	75	155	0	1695	35.88	11.59	385	67	4
17	70	30	12	600	34.32	7.94	...	69	4
19	70	30	12	600	28.70	11.88	417	70	4
23	70	30	12	600	20.44	10.67	334	71	4
24	70	30	12	600	18.74	.....	375	72	4
29	70	30	12	600	7.38	11.75	319	72	4
1923									
Jan. 3	70	30	12	600	9.23	10.79	306	69	4
7	70	30	12	600	+	11.83	226	67	4
11	70	30	12	600	0	13.44	166	69	4
14	70	30	12	600	0	11.49	183	69	4

TABLE IV.—CASE NO. 229

Date, 1922.	Diet: P. gm.	F. gm.	C. H. gm.	Cal.	Glycosuria, gm.	Plasma sugar mg. per 100 cc.	Weight, pounds.	Insulin units.
Oct. 3	15	0	15	120	++++	359	36	2
6	15	0	15	120	+	206	38	2
8	15	0	15	120	0	168	39	3
10	15	0	15	120	0	123	..	3
12	30	28	5	400	0	....	38	3
13	30	28	5	400	+	429	40	3
15	30	28	5	400	+	385	40	5
17	30	28	5	400	+	385	38	5
19	30	28	5	400	++++	429	..	5
22	30	28	5	400	++	318	39	5
23	30	28	5	400	+	357	..	5
24	30	28	5	400	+	405	37	5
29	30	28	5	400	0	270	36	8
Nov. 1	30	28	5	400	0	263	38	8
2	40	44	10	600	0	....	..	8
3	40	44	10	600	0	....	37	8
4	40	44	10	600	+	326	35	8

Remarks on Table IV. This ten-year-old girl on a semistarvation ration of 15 gm. protein and 15 gm. carbohydrate, without fat, with first 2 and then 3 units of insulin per day, became free from glycosuria and her high plasma sugar fell to 0.123 per cent.

October 12. The diet was changed to 30 gm. protein, 5 gm. carbohydrate and 400 calories. Glycosuria began with unusual promptness and continued until insulin dosage was increased to 8 units on October 29. This case was so severe that the harmfulness of even a small fat allowance, which probably raised the actual fat combustion little if at all as compared with the fast, could be demonstrated with unusual quickness and ease.

November 2. The diet was further increased to 40 gm. protein, 10 gm. carbohydrate and 600 calories. Glycosuria began the following day, doubtless in part because of the slight increase in carbohydrate and protein.

TABLE V.—CASE NO. 1274

Date, 1922.	Diet: P. gm.	F. gm.	C. H. gm.	Cal.	Glycosuria, gm.	Plasma sugar mg. per 100 cc.	Weight, pounds.	Insulin units.
Nov. 23	25	5	10	185	O	366	105	6
26	25	5	10	185	O	234	105	6
29	25	5	10	185	O	185	107	6
30	40	20	10	380	O	....	109	6
Dec. 2	40	20	10	380	O	112	111	6
3	80	25	10	585	O	125	111	6
4	80	25	10	585	O	102	114	6
6	100	25	10	665	O	....	116	6
7	100	25	10	665	O	62[1]	116	6
9	200	25	10	1065	O	87[1]	115	6
10	200	25	10	1065	O	112	109	6
11	200	25	10	1065	O	175	....	6
12	300	25	10	1465	O	203	111	6
14	300	25	10	1465	O	230	113	6
15	300	25	10	1465	O	238	....	9
18	300	25	10	1465	O	92[1]	114	9
19	300	25	10	1465	O	175	....	9
22	90	111	25	1465	O	209	112	9
28	90	111	25	1465	O	178	111	9
29	90	111	25	1465	O	209	....	9
1923								
Jan. 1	90	111	25	1465	O	168	106	9
3	90	111	25	1465	O	....	106	9

[1] Blood sample taken at 8 P.M.

Remarks on Table V. In the preceding experiment the protein ration was changed somewhat, and it is desirable to investigate the influence which some authors have attributed to protein, whether derived from the

diet or from the body tissues. The present patient, with 6 units of insulin per day, was free from glycosuria on the low diets first shown and the plasma sugar was steadily falling. Beginning December 1 he had well-marked hypoglycemic symptoms every evening, though not severe enough to require special treatment. These symptoms were not prevented by an increase of protein to 80 gm. on December 3, to 100 gm. on December 6, or to 200 gm. on December 9, though the plasma sugar rose slightly in analyses taken mornings before breakfast.

December 12. A further increase to 300 gm. protein stopped the hypoglycemic symptoms and produced hyperglycemia. An increase of insulin to 9 units daily, beginning December 15, reduced the plasma sugar somewhat.

TABLE VI.—CASE NO. 989

Date, 1922.	Diet.				Glycosuria, gm.	Plasma sugar mg. per 100 cc.	Weight, pounds.	Insulin units.
	P. gm.	F. gm.	C. H. gm.	Cal.				
Sept. 1	60	115	30	1400	++	312	....	7
2	60	115	30	1400	+	200	36	7
3	60	115	30	1400	O	....	....	7
4	60	115	30	1400	6.0	306	36	7
5	60	15	40	535	5.3	306	....	7
6	60	15	40	535	1.9	....	36	7
7	60	15	40	535	3.3	283	....	7
8	60	15	40	535	4.0	....	36	7
9	60	15	40	535	4.8	250	....	7
10	60	15	40	535	4.8	....	36	7
11	60	15	40	535	O	195	....	7
12	60	15	40	535	O	....	36	7
13	60	15	40	535	O	157	....	7
14	60	15	40	535	O	....	36	7
15	60	15	40	535	O	....	36	7
16	60	15	40	535	O	203	36	7
17–18	60	15	40	535	O	....	....	7
19	60	15	40	535	O	126	36	7
20	60	15	40	535	O	....	....	7
21	60	15	40	535	O	139	36	6
22–23	60	15	40	535	O	....	....	6
24	60	15	40	535	O	137	36	6
25	60	115	30	1400	O	....	....	6
26	60	115	30	1400	O	....	36	6
27	60	115	30	1400	O	....	....	6
28	60	115	30	1400	1.4	226	36	10
29	60	115	30	1400	+	....	....	12
30	60	115	30	1400	O	....	36	14
Oct. 1	60	115	30	1400	+	....	....	16
2	60	115	30	1400	O	....	36	16
3	60	115	30	1400	O	....	....	18
4	60	115	30	1400	O	164	36	18
5	60	115	30	1400	O	....	....	18
6	60	115	30	1400	O	....	37	18
7	60	115	30	1400	O	....	37	18

Beginning December 22, the protein was reduced to 90 gm., the carbohydrate increased to 25 gm. and the fat increased so as to keep the total calories unchanged. This diet was lower in both its nitrogen and its glucose content as compared with the preceding, but yet the tendency to glycosuria or hyperglycemia seemed to be scarcely changed, inasmuch as the total calories were kept constant. The influence of the high protein in turning hypoglycemia into hyperglycemia seems to be explainable chiefly by the increase of calories involved.

Other experiments (reported by Dr. Sherrill) show that the glycosuric influence of protein has actually seemed greater than that of the caloric equivalent of fat. In descending order of glycosuric influence the foods are first carbohydrate, second protein and third fat when the comparisons are based upon equal caloric quantities. The influence of protein, however, is distinctly less than its theoretical glucose content, as judged either by the causation of glycosuria or the prevention of hypoglycemia. The ideas of authors who have assumed a specially powerful action of protein, through its specific dynamic effect or through unknown toxic processes, are by no means substantiated by such experiments.

Remarks on Table VI. We may investigate next to what extent an explanation can be based on the glucose value of the diet which a number of authors have regarded as the sole factor governing the insulin requirement. In this ten-year-old girl hyperglycemia and glycosuria had been produced by a diet of 60 gm. protein, 30 gm. carbohydrate and 1400 calories, with 7 units of insulin per day.

September 5. The protein was left unchanged, the fat was reduced by 100 gm. and the carbohydrate was increased by 10 gm. Theoretically the glucose value of the diet was thus kept constant, but the calories were reduced to an undernutrition level of 535. With the same insulin dosage, glycosuria was absent after September 10, and by September 24 the plasma sugar had fallen nearly to normal.

Beginning September 25 the original diet of 1400 calories was resumed. Glycosuria appeared September 28, notwithstanding the increased insulin dosage. It was halted when the insulin was increased to 16 units on October 1, but a further increase to 18 units did not suffice to restore the previous low level of blood sugar.

Remarks on Table VII. In this case glycosuria was absent but hyperglycemia present on an undernutrition diet of 40 gm. protein, 24 gm. carbohydrate and 346 calories, with 6 units of insulin per day.

Beginning November 19 the fat was increased by 150 gm., so as to raise the total calories to 1696. Glycosuria began on November 23, and during the following month reached high amounts, notwithstanding the increase of insulin dosage. An increase of insulin to 28 units on January 14 finally made the urine free from sugar after January 18, but a further increase to 32 units of insulin daily failed to reduce the plasma sugar below 0.2 per

TABLE VII.—CASE NO. 1073

Date, 1922	Diet: P. gm.	F. gm.	C. H. gm.	Cal.	Glycosuria, gm.	Plasma sugar mg. per 100 cc.	Weight, pounds.	Insulin units.
Nov. 11	40	10	24	346	+	....	112	4
12	40	10	24	346	○	....	111	6
14	40	10	24	346	○	195	110	6
16	40	10	24	346	○	156	112	6
17	40	10	24	346	○	182	....	6
19	40	160	24	1696	○	195	111	6
23	40	160	24	1696	++	312	112	6
Dec. 1	40	160	24	1696	++	326	113	6
10	40	160	24	1696	57.83	349	113	0
12	40	160	24	1696	18.64	....	113	10
14	40	160	24	1696	36.21	405	113	10
17	40	160	24	1696	20.25	....	....	14
21	40	160	24	1696	37.59	374	114	14
23	40	160	24	1696	15.37	....	....	18
27	40	160	24	1696	4.76	349	116	18
1923								
Jan. 4	40	160	24	1696	10.69	....	118	20
5	40	160	24	1696	8.93	306	116	20
7	40	160	24	1696	11.00	349	116	22
10	40	160	24	1696	20.49	....	....	24
11	40	160	24	1696	18.80	385	116	24
14	40	160	24	1696	5.77	....	....	28
16	40	160	24	1696	+	319	119	28
17	40	160	24	1696	+	246	120	28
18	40	160	24	1696	+	....	....	32
19	40	160	24	1696	○	238	120	32
21	40	160	24	1696	○	200	....	32
23	40	160	24	1696	○	206	....	32

cent. In this case the quantities of sugar excreted and also the increase of insulin requirement from 6 to 32 units are too great to be explained by any quantity of sugar that could possibly be derived from the 150 gm. fat that was added.

Remarks on Table VIII. This patient had become free from glycosuria on a diet of 55 gm. protein, 50 gm. carbohydrate and 800 calories, with 21 units of insulin per day.

Beginning February 17 the fat was increased by 133 gm. so as to raise the total calories to 2000, while the protein and carbohydrate were left unchanged. Glycosuria quickly appeared and rose to the neighborhood of 80 gm. per day, notwithstanding the increase in insulin dosage. It was stopped only when the insulin was increased to 45 units on March 8. In this experiment also the quantities of sugar excreted and the increase of insulin requirement from 21 to 45 units are too great to be accounted for by any glucose possibly derived from the 133 gm. of added fat.

TABLE VIII.—CASE NO. 823

Date, 1922.	Diet: P. gm.	F. gm.	C. H. gm.	Cal.	Glycosuria, gm.	Plasma sugar mg. per 100 cc.	Weight, pounds.	Insulin units.
Feb. 15	55	42	50	800	O	....	....	21
16	55	42	50	800	O	....	92	21
17	55	175	50	2000	O	198	....	21
18	55	175	50	2000	+	....	96	24
19	55	175	50	2000	+++	407	....	24
20	55	175	50	2000	++++	....	96	24
21	55	175	50	2000	81.07	....	....	27
22	55	175	50	2000	80.85	349	98	27
23	55	175	50	2000	63.64	....	....	27
24	55	175	50	2000	40.04	....	98	27
25	55	175	50	2000	31.61	....	....	30
26	55	175	50	2000	63.00	416	100	30
27	55	175	50	2000	37.76	....	....	30
28	55	175	50	2000	71.28	....	....	30
Mar. 1	55	175	50	2000	79.00	416	101	36
2	55	175	50	2000	36.86	....	....	36
3	55	175	50	2000	64.24	....	102	36
4	55	175	50	2000	27.03	....	102	40
5	55	175	50	2000	8.13	....	....	40
6	55	175	50	2000	57.67	319	103	40
7	55	175	50	2000	25.85	....	....	40
8	55	175	50	2000	5.32	405	103	45
9	55	175	50	2000	O	....	....	45
10	55	175	50	2000	O	90	104	45

The experiments with direct quantitative measurement of the insulin requirement, therefore, confirm in all respects the previous experiments with regard to the influence of fat and total calories upon diabetic symptoms. The influence of body weight is demonstrable with equal plainness. Our most striking illustration is furnished by two children of similar age and height. The boy, No. 1034, has distinctly the more severe diabetes, because it was impossible to stop his glycosuria by any degree of fasting or undernutrition, and he was studied by Drs. Du Bois and Richardson in the Russell Sage Institute as an example of unusually severe diabetes with high D to N ratios. The girl, No. 989, had a decidedly less severe condition, because she slowly acquired tolerance to the extent of 50 gm. protein, 15 gm. carbohydrate and 1000 calories before the use of insulin. With insulin her diet was gradually increased to 60 gm. protein, 100 gm. carbohydrate and 2000 calories, and for the assimilation of this she has required 70 units of insulin per day, which is the highest dosage we have given regularly to any patient in our series. The boy has recently been placed upon identically the same diet and has kept free from glycosuria, with only 28 units of insulin per day. The difference is that the girl's

weight was built up to over 60 pounds and she is actually somewhat obese. The boy was kept undernourished, so that his weight is only 40 pounds. We thus have at present the seeming anomaly that he with his more severe diabetes has only a fraction of the insulin requirement of the girl for the assimilation of the identical diet. His requirement will doubtless increase as his weight rises, unless the condition is altered by a marked gain in his own pancreatic function.

Still other questions can be answered with the aid of insulin. The fear has been expressed that too great undernutrition may actually reduce the patient's tolerance, either through the influence of systemic weakness upon the pancreatic island function or through the excessive catabolism of body protein when the fat reserves are reduced too low. It is easy to show that undernutrition tends to reduce the insulin requirement, irrespective of the extreme to which it may be carried. In one instance we produced a hypoglycemic reaction to the extent of complete unconsciousness in an extremely emaciated diabetic man with a dose of only 0.5 unit of insulin. With increase of diet and weight this patient has since taken as much as 60 units of insulin per day. If any point of undernutrition can be found at which increase of diet with fat or any other food reduces the insulin requirement, or reduction of diet or body weight increases the insulin requirement, such observations will be highly important and should be published. We feel justified in the extreme undernutrition to which we have subjected patients with extremely severe diabetes, by the demonstration that such undernutrition reduces the insulin requirement to a small fraction of the requirement which is found with higher levels of diet and weight, and thus can enable these patients to maintain life with a minimum remnant of pancreatic island function.

Another question which can be answered is in regard to the use of hyperglycemia or glycosuria as indications of overstrain of the island function. It is now a perfectly simple matter to show that a certain dose of insulin is necessary for stopping glycosuria and a distinctly higher dose is necessary to reduce the blood sugar to normal. The difference between these two doses may range from 2 to 6 or more units per day in different cases, and this difference is the measure of the degree to which the pancreatic islands have been overstrained in their function by the persons who have been content merely to keep the urine sugar-free and allow marked hyperglycemia to persist. Gradual downward progress is, of course, to be expected from such overstrain in all cases which are seriously progressive in character, particularly those in youth. The insulin treatment promises to add strong evidence to the principle which I have demonstrated to my own satisfaction with strict diet treatment—namely, that diabetes is not inherently progressive and that downward progress results practically altogether from functional injuries.

In summary, the important fact proved by these experiments is that the insulin consumption of the organism is governed not merely by glucose but also by the total calories of the diet and by the body weight. The clinical importance of this principle is obvious, for the limitation of the total diet and body weight within moderate limits is the most effective means of avoiding the need for excessive insulin dosage and its attendant difficulties and dangers. The theoretical importance is clearly great, and by paying attention to the powerful influence of the general nutritive level which we physicians have known for years, chemists and physiologists may be saved from basing their investigations of insulin upon false premises of relation to glucose alone. There is as yet no decisive information whether insulin is concerned directly in the metabolism of all foods, or whether there is merely an indirect connection in the sense that other foods and the body weight somehow modify the utilization of glucose.

DISCUSSION ON THE PAPERS OF DRS. McPHEDRAN AND BANTING, JOSLIN, FOSTER AND ALLEN

Dr. Reginald Fitz, Boston: In dealing with hospital patients, diabetes and its treatment is a severe economic drain upon the patient and upon his family, necessitating special equipment and food, and accompanied by progressive loss of strength under the best of circumstances. What are we to advise such patients in regard to insulin? Are they to disregard expense and to procure enough insulin to make themselves comfortable? By so doing can they regain normal health and efficiency? Or is insulin at present a luxury rather than a necessity?

Dr. Russell Wilder, Rochester: The problem of balancing diet in young children calls for careful handling, especially when cases are complicated by infection. The balance between hypo- and hyperglycemia in the child is so narrow that it is easily upset either way. In such cases at least I agree with Geyelin that it is well to have a buffer in the form of some glycosuria and hyperglycemia. This provides a margin of safety.

With reference to Dr. Allen's report, apparently no account is taken of the total calorie requirement. Unless this is exactly satisfied, conclusions obtained from the dietary data are unwarranted. This has been repeatedly emphasized.

Dr. Alfred Stengel, Philadelphia: In regard to the treatment of these patients my experience is the same as that of the other speakers. We have treated patients who have been already treated by other methods. The patients were greatly reduced in weight. They put on a good deal of weight by taking a larger diet and large doses of insulin. I think in some

of these cases a slight spilling over of sugar might be advantageous. A gradual reduction of blood sugar might be effected, keeping the urine as free of sugar as possible; perhaps on 2000 calories they may be kept sugar-free. Most of my patients have been adults. I have treated very few children. The children were treated on the older methods, with greatly reduced carbohydrates and low fat.

There are other factors in diet besides sugar which must be considered, and in looking at the tables set forth by Dr. Allen I noticed that he suddenly throws into the diet a large quantity of fats—on one day there are 800 calories and on the next day 2000 calories. That is not a very fair test of metabolic processes. We should not consider what fat is swallowed but what is actually metabolized. There might be considerable digestive disturbance with this sudden addition of fats. In my series of 50 cases we have taken the adolescent cases and given them 50 per cent above maintenance requirements, so that they regain strength, and later take up a program of restriction in diet to send them out with the minimal dosage of insulin that will hold them sugar-free.

Dr. E. P. Joslin, Boston: Infection is the worst risk to the diabetic. If he gets to the hospital alive then we can take care of him. If the surgeon thinks the patient can stand operation, it is done that night. In regard to coma, I agree with Dr. Foster in every detail. It is important to treat the dryness of the patient. Coma is a terribly serious disease and we should not lose any time; the patient should have liquid right away. This can be given by subcutaneous injections of 1000 cc salt solution and then gradually working in fluids by other means. The first hour is worth more in treatment than the next twenty-four hours. In regard to hyperglycemia and glycosuria, these patients in middle life die from the complications, and if you only prolong their lives to get complications later from high blood sugar you are not doing the best for them. I believe in keeping them sugar-free, not only by insulin but by proper dietary restriction and slow growth. In regard to insulin as a luxury versus a necessity, that is a very important point. School-teachers can work with insulin when they cannot without it, so that is an economic benefit to one class. I think we should all collect data on this question and present them at our next meeting. In regard to alkalis, I have not been giving them since 1917. Dr. Boch says that only 10 per cent of the cases need it. I believe it is my duty to treat my cases as I have done for the last six years. If I have had fair results without insulin and without alkalis, it is interesting to look forward to what will happen with the help of insulin.

Dr. N. B. Foster, New York: In regard to the economic questions arising with the use of insulin, patients are able with its help to work and

support their families, while without it they could not work at all. In regard to raised diet and insulin, a man on 1000 calories was reduced to 110 pounds' weight. He is now receiving 15 units and can take 2200 calories and weighs 140 pounds.

Dr. H. Rawle Geyelin, New York: There are various factors to be considered: (1) the cost of the insulin; (2) the fact that after a time decreased amounts of insulin are necessary to keep the urine sugar-free on the same amount of carbohydrate. Dr. Joslin has figures to show that the cost of the dietetic dietary per day when added to the cost of the diet of the household is as much as the cost of insulin to the patient and his family. When the patient takes the proper amount of insulin he can take the same food as the rest of the community. Adults are brought back to increased earning capacity. Insulin, therefore, cannot be regarded as a luxury but as an absolute necessity.

In regard to allowing sugar to appear in the urine, most of the high peaks of sugar in the urine were concomitant with some minor infection, and control could be kept of the urine when there was no disturbing process going on. In experiments in which the blood sugar was determined at regular intervals both day and night, even in cases where there is no sugar apparent in the urine, there are individual specimens where the blood sugar is normal during the day and does not begin to go up until 4 in the morning, although the period during which hyperglycemia and glycosuria exists is not very long. There is no positive evidence that hyperglycemia itself is conducive to concomitant infection; we have assumed that, but it is not proven. Another thing that has a bearing on the question of insulin is the human problem. If one sees the expression on the faces of these youngsters when allowed to eat mashed potatoes for the first time, one realizes that insulin is worth while.

Dr. F. M. Allen, New York: Dr. Foster's remark really pertains to a different subject. His patient evidently developed an actual increase of tolerance under insulin treatment. We have observed a number of such improvements as mentioned by Dr. Banting and Dr. Geyelin, and it is important that the interpretation of prolonged experiments should not be confused by this factor. Control is, of course, possible by a reduction of the diet and body weight, which will be found to reduce the insulin requirement. In other words, the reduced need for insulin in such a case can be shown not to be due to the increase of weight but to be the result of an improvement of pancreatic island function in spite of the increase of weight.

Dr. Stengel's criticism partly is answered by our numerous nitrogen analyses, which cannot be shown in these few lantern slides and partly

runs opposite to his own argument. As a matter of fact, no digestive disturbances have occurred in the emaciated diabetics who have been allowed liberal diets. If there were any deficiencies of absorption, however, they would mean merely that the quantities of protein or other foods metabolized were less than the quantities fed. If these smaller quantities produce the results observed these results are all the more striking.

Dr. Wilder is not correct in supposing that any point of criticism has been left open by the lack of determinations of the total metabolism. In the first place the effects shown are independent of such determinations. These are the effects which are produced in diabetics when certain diets are fed. Respiration experiments may be interesting if they can show why these results are produced, but they cannot alter the facts. In the second place, it will be observed that the experiments have been planned so as to make overallowances for any possible difference between materials fed and materials metabolized. With low diets of perhaps 300 calories, it is certain that body fat and probably body protein are burned in addition to the food. With the highest diets employed it is certain that less material was metabolized than was fed, because the patients gained weight. It is all the more remarkable that the differences between high and low diets are so sharply demonstrable under these circumstances. The same statements apply to the previously published experiments without insulin.

Dr. F. G. Banting, Toronto: I am very glad to have had the honor of representing the Toronto group at this Association, and sorry that the other members of the group have not been present to speak here. I should like to acknowledge to this society the credit due to Dr. Best and Dr. Cobb for their painstaking work, and also thanks to Prof. J. J. R. Macleod, in whose laboratory facilities were given us for our experimental work in the physiological part of the investigation. The physiological side must precede the clinical work. The Eli Lilly Company have done very good work and have aided greatly in making possible the production of insulin on a large scale. There were many and great difficulties in the way of production which had to be overcome, and magnificent work has been done along this line. In the whole program of work there has been admirable coöperation along all lines. There is no doubt now that the greatest advancement will be reached by progress in the line of production of the drug and reduction of cost, and this is being gradually accomplished. We hope that in the near future the matter of purchase of insulin will be taken up by the Government and by the public health authorities, so that needy patients may be treated free of cost or for a very small sum.

In regard to the various points mentioned in the discussion, I would say that at the present time if a patient becomes sugar-free on a basal requirement diet he is not considered a sufficiently severe case of diabetes for

insulin therapy. Later, when the supply of insulin is more obtainable, less severe cases may be given the benefit of treatment. We define severe diabetics as those persons unable to metabolize sufficient carbohydrate, fat and protein to carry on an ordinary useful life. Insulin treatment consists of a balance between the amount of artificially administered insulin and the amount of sugar that cannot be handled by the patient's own pancreas. In milder cases it is administered once a day; in moderately severe cases, twice; in very severe cases, three times a day. It is best administered twenty minutes to one-half hour before each meal.

When carbohydrate enters the blood it causes stimulation of the internal cells of the pancreas to metabolize the carbohydrate of the food. Insulin is absorbed by the skin and enters the circulation, a sufficient quantity being given to balance the hypoglycemia of the insulin with the hyperglycemia of the meal. The art of insulin treatment is in maintaining this balance to a nicety. A patient with a very high blood sugar will stand a comparatively higher dose, because the blood sugar must be reduced to normal. In regard to quantity, roughly speaking, one unit of insulin in moderately severe cases of diabetes utilizes 2.5 grams carbohydrate; in the less severe cases more carbohydrate is accounted for. In the management of the case the diet is decreased and the dosage increased until the amount of food required by the patient is reached. The diet is then kept constant, and sufficient insulin is given to maintain the patient sugar-free if possible.

In regard to the question as to whether or no glycosuria is injurious to the diabetic, the answer is not known at the present time. It is true that patients can go along without feeling ill when excreting small quantities of sugar, but it is more normal to keep a patient sugar-free by careful balancing of the factors. This is a difficult matter in severe cases, and most difficult of all in children, because the margin is very narrow between hypoglycemia on the one hand and hyperglycemia on the other. In the diabetic of long standing, where the kidney threshold is high, there is a wider margin of safety, and the case is much more easily handled.

Insulin shock is a definite entity. It is always recognizable, and the subjective symptoms are pathognomonic of the lowered blood sugar. The reactions depend on the fall of the blood sugar and the extent and rapidity of that fall. The reactions occur when the blood sugar falls below a certain point of normality, which, however, is not constant for all individuals.

We have been able to make use of some experimental work done on rabbits and apply it clinically in our work at the Children's Hospital in Toronto. It was found that calcium administration relieved the hypoglycemic convulsions in rabbits even without an attempt to raise the blood sugar. It has been worked out as a result of this that a dosage of 3 grams of calcium lactate three times a day will render children less likely to suffer

hypoglycemic convulsions when receiving insulin therapy. Another point is that diarrheal patients, formerly extremely difficult and discouraging to treat with insulin on account of the likelihood of hypoglycemic convulsions, are less likely to show these symptoms when treated with calcium chloride as well. In some of these cases, however, the patient becomes progressively worse.

In regard to the question as to whether these patients will need insulin permanently. Insulin treatment relieves the strain on the pancreas and puts it on a more normal basis, so that in a few months patients are able to take additional calories without increased dosage. It is noted that those patients who remained acetone-free despite starvation tend to obtain an increased sugar tolerance after a time.

Insulin is not, as has frequently been quoted, a "cure" for diabetes, but it is a treatment; it allows the patient to combat infections, to overcome acidosis and coma; it permits him to burn sufficient carbohydrate so that proteins and fats can be added to the diet, and thus it allows him to acquire sufficient energy to carry on his work in the ordinary walks of life. This, it seems to me, is an answer to the question whether insulin is a luxury or an economical necessity.

THE CLINICAL SIDE OF THE CONDITION SPOKEN OF AS A MASSIVE COLLAPSE OF THE LUNG

By NORMAN B. GWYN, M.B.
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In any discussion upon massive collapse of the lung, the statement is usually made that it occurs too rarely to deserve practical consideration, yet Elliott and Dingley[1] speak of seeing 11 striking instances thereof in two years, Scrimger[2] and Hirschbroek[3] met with 7 and 3 cases respectively in one year, Pasteur[4] deals with still larger numbers and the journals of today show that the condition is being met with when looked for. Its clinical symptoms—urgency of respiration, cough, distress, with cyanosis and prostration—are the symptoms of most of the acute accidents which befall the lungs and heart, and it is safe to say that behind the diagnosis of pneumonia, pleurisy, pulmonary embolus, acute cardiac failures or acute pneumothorax* have lain many unrecognized cases of massive collapse. As Pasteur states, before 1908, it was not spoken of, now it is tabulated in some hospital statistics as occurring fourth in order among the respiratory complications of surgical procedures.

Though most often seen following abdominal operations or chest wounds, massive collapse makes appearance under other circumstances and is an accident to be thought of as occurring in pulmonary affections and in conditions obstructing the air passages: Death on the operating table subsequent to vomiting and aspiration of food particles was the history in 1 case whose lungs were found completely collapsed; Pasteur's early recorded cases had been described as occurring in the course of diphtheria and had seemed

* The overdistention of the sound side may at the first sight make the suggestion of pneumothorax to the observer.

to be due to diaphragm paralysis; an earlier description (the first description of the condition), by Pearson Irvine,[5] is of upper lobe collapse in association with paralysis of the upper muscles of respiration, a sequel of diphtheria. Singularly few references to acute complete massive collapse are to be found up to 1914. Partial and more slowly developing collapse, associated with pressure from aneurysm, tumor, enlarged heart and pericardium, or with effusions into the chest cavities, is better known but still hardly enough considered.

In a case of pneumonia, seen in 1911, the following notes were made:

"White woman, aged sixty years, usually in good health. Outspoken consolidation of lower lobe on right side. Temperature falling, but no resolution at end of two weeks, and clear, dry, tubular breathing remains." On the nineteenth day there developed a sudden attack of intense dyspnea, lasting nearly six hours, and the patient became desperately ill. On examination it was noted that the whole upper right front was sunken; looked as if collapsed; was completely dull to percussion and had lost all signs of breath sounds. *The heart was seen beating to the right of the sternum;* could be felt in this situation and gave no indication of its presence to the left of the midline. The left front chest was distended, so hyperresonant that pneumothorax was suggested; the clear breath sounds, the good expansion, the normal fremitus indicated, however, that the acute happening was on the other side. The severity of the symptoms waned by the end of six hours, tubular breathing replaced the hidden sounds of the area, which was now considered to be a massive collapse of the whole right upper lobe. In two days the heart was noted as returning to its proper position, and in a week the physical signs of collapse and consolidation had disappeared from all lobes. In this case there had been no cough or expectoration; the onset of a rapid heart-rate was observed at the beginning of the acute symptoms. The general state of the heart, however, seemed good and the patient made a complete recovery.

Two years later this happening was reproduced in an elderly white man:

He had been admitted to the ward with aortic stenosis and had developed pneumonia of the right lower lobe. Early in the disease (the fourth day), sudden, acute aggravation of symptoms took place with urgent dypsnea, and it was noted "that the right front was sunken in, was now

quite flat to percussion, that the vocal fremitus in this situation was diminished and that the breath sounds had disappeared." Familiar now with Pasteur's descriptions, it was easy to detect the lack of expansion of the lung lobe and to place the heart to the right of the sternum. The overexpansion of the left side was not so much in evidence in this second case, the symptoms were never so distressing, they lessened in the course of a few hours and in five days *the apex had reëxpanded and was resonant before the clearing of the lower lobes.* In this patient there had been abundant, sticky, rusty expectoration from the beginning of the pneumonia. The heart-rate during the acute respiratory distress never exceeded 90; there were frequent omissions of ventricular cycles, but a rapid convalescence was not interfered with. We were unable to get *x*-ray pictures in these cases.

In 1917, there occurred the chance to get a picture of what had seemed to be an acutely developing collapse of the left base in a case entering as consolidation of the left lower lobe. The urgency in this patient had no approach to that seen in the two instances of upper lobe collapse in pneumonia, but was noticeable enough to require investigation, though it is probable that the main features of the condition had begun to pass off by the time of his admission. Not only were the classical physical signs in evidence (consolidation of the lung, dislocation of the heart into the affected side), but it seemed that the attempt of the chest to compensate for the retraction of the lung could be demonstrated in the pushing in of the lateral wall of the thorax and in the obliquity of the ribs of the affected side. The following notes were made:

Allistone, admitted, July 1, 1917: collapse or pneumonia of the left base. Man had been ill for a few days with respiratory distress and fever. During the night there took place a sudden accession of the breathlessness, and an examination showed that the whole left lower chest was fallen in and retracted (Fig. 1). The heart, which had been reported upon as showing no variations from normal save a slight increase in rate, was now found much displaced to the left with its impulse one inch to the left of the nipple. At the left base the area of dulness had increased, vocal fremitus was present, the breath sounds were more harsh than tubular, there were many moist rales and the voice sounds were of nasal quality. Improvement of all symptoms ensued in a few hours; a few days sufficed to clear the chest and the patient was evacuated with a restored contour, a cleared lung and a heart beating inside the nipple line.

Writing in the *Journal of Laryngology, Rhinology and Otology* for September, 1918, C. H. McIlwraith,[6] of St. Clair Thompson's clinic, describes the unusual condition of a complete collapse of both lungs occurring in a child, aged twenty-two months, whose larynx had become obstructed by papillomatous growths.

FIG. 1.—*X*-ray photograph of patient with collapse or pneumonia of left base. History is detailed above. Acute onset of respiratory distress; signs of consolidation at left base; large heart area, and heart and mediastinum displaced to the left toward area supposed to be collapsed. The falling in of the side of the chest is evident, as well as the falling in of the ribs themselves, representing an attempt to compensate the negative pressure in the chest. Right side gives but little indication of a mediastinal shadow.

Fourteen days of difficulty on both inspiring and expiring had made necessary the performance of an operation for the removal of some of the growths. No lessening of the dyspnea had followed and tracheotomy was done. Even this operation gave no relief, and it was noted that but little air was entering the chest. The child died, cyanosed, eighteen hours after the second procedure. Complete collapse of both lungs was found, *with no pneumothorax*, the larynx was the seat of many small growths; the trachea was clear and the bronchi were not obstructed; air in the tissues of the neck and mediastinum was considered to have been drawn into these tissues from the tracheotomy wound.

McIlwraith considers the case unique: (1) Because of the extent of the collapse; and (2) because the conditions seemed to confirm

the old ball-valve theory of collapse, a possibility in this case where so many hours of struggle had elapsed before the fatal issue.

Equally unique but more striking in the suddenness of its appearance was the collapse of the lungs occurring in a case of Dr. Wookey, of the Toronto General Hospital staff.

FIG. 2.—A complete collapse of both lungs which followed obstruction of the trachea and bronchi. The case of Dr. Wookey above referred to.

Radium applications to an angeioma of the lip had produced a large slough, a severe hemorrhage had taken place and both facial arteries were being ligated under general anesthesia. The operation required but a few minutes and the patient seemed in good condition when taken off the table. Two or three minutes later she stopped breathing; Dr. Wookey opened the trachea and found it full of food material. All attempts to induce respiration failed. The lungs were found completely and solidly collapsed as pictured; one bronchus was firmly blocked; there was no pneumothorax (Figs. 2 and 3).

These cases may be taken as demonstrating that massive collapse of a lobe, a lung or both lungs is a condition to be thought of as occurring in connection with disorders more purely of the air passages and lungs, apparently in the two latter cases the more complete the tracheal or bronchial obstruction the more rapid and active the collapse of the lungs.

More often met with, and, as Pasteur insists, met with when looked for, are the instances of collapse of lower lobes following

FIG. 3.—Microscopical section of the lung pictures in Fig. 2. The completeness of the collapse is apparent.

some operation, usually an abdominal one. Shortly after the operation (in one of our cases even before completely out of the anesthetic) the patient may show sudden signs of great respiratory urgency;† pain in the side affected may be complained of; there may be cough, and usually there has been the history of expectoration of colorless sputum. When looked for, the physical signs may be very definite: Retraction of the side affected; dislocation

† The early onset of the symptoms with the rapid development of physical signs is something quite out of keeping with the development of the ordinary inflammatory lesion of the chest. Fig. 3, a section from the lung of Dr. Wookey's case show how rapidly complete a collapse may be.

of the heart *to that side;* and signs of consolidation—though the latter finding may not be clear at first, hidden sounds taking the place of tubular breathing. Moisture may or may not be in evidence and the signs of consolidation may vary much from day to day. Overexpansion of an upper lobe or of the whole lung on the sound side may occur rapidly. Recovery and a quick clearing of the collapse picture is the rule, though two weeks may elapse before the chest seems normal. The detail of one of Hirschbroek's cases is of particular value: Both lower lobes were involved and the patient died. Collapse with no evidence of pneumonia was the finding.

At a time when one Canadian base hospital was paying attention to general rather than to war surgery, 3 outspoken cases of collapse of a lower lobe following abdominal operations were seen within a period of five weeks. All were urgent in their suddenly developing dyspnea, 2 looking as if they could under no circumstances survive. In 1 the symptoms appeared as he was coming out of the anesthetic; in the others some eight to ten hours later. Two had severe pleural-like pain and all had cough, mucoid expectoration, fever and rapid pulse. Six to twenty-four hours saw the disappearance of the most severe of the symptoms; in ten to twenty days the lobe had reinflated and the heart was back in place. Important was the note, in 2 of these cases, that signs of bronchitis had existed before the operation. The details of their clinical history may be given.

Case I.—*Collapse of lung following abdominal operation.* Whitman, Private, G. R. No. 469326, P. C. L. I., aged twenty years. Admitted to No. 1 Canadian General Hospital on November 12, 1917, with a history of pain over the right iliac region for six days, and with vomiting and loss of appetite. Had had a similiar attack three years ago. Temperature, 99°; pulse, 104.

On examination there was pain over the region of the appendix on deep palpation, but no rigidity or signs of any acute inflammation. These symptoms persisted for three days.

Appendectomy was performed under ether on November 16, 1917, and a moderately inflamed appendix surrounded by adhesions was found; the wound was closed without drainage. When seen toward evening, while recovering from the anesthetic, the patient was complaining of a

sharp pain over the front of the right chest, he had much dyspnea and a cough. Examination early the next day showed dulness at the right base with tubular breathing, and a tentative diagnosis was made of collapse with bronchopneumonia. Owing to the urgency of symptoms nothing more definite was made out.

November 18, the patient was transferred to the medical ward. Temperature and pulse were both high. He had considerable dyspnea. Examination of the chest showed much lagging of the right side, with slight hyperresonance in the upper front. Vocal fremitus was much increased and the breath sounds were very distant but vesicular in nature. Behind, on the same side, there was dulness in the lower half, with very weak breath sounds and vocal fremitus. Over the upper lobe, behind, there was resonance and fairly strong breath sounds. The left side showed harsh breathing only. The heart was almost entirely displaced to the right of the sternum; it could be seen beating in the fourth interspace just inside the right nipple and percussion showed dulness as far out as the nipple. No heart sounds were to be heard on the left side.

November 20. The signs in the chest had changed entirely; there was now solid dulness on the right side up to the clavicle; the vocal fremitus was very weak. Breath sounds were amphoric. The vocal resonance was nasal and very much increased; the heart was still totally displaced to the right.

General condition of the patient was fairly good; he complained of much pain and tightness over the front of the right chest and had a moderate amount of loose, mucoid sputum. Temperature was high.

November 22. General condition improved; chest signs had changed again; they were now exactly the same as on the first examination; left base also showed some slight dulness.

November 23. Chest signs showed still another change, breath sounds were amphoric; the vocal fremitus was weak and the note was wooden; a few fine crepitations were also heard.

November 24. Considerable improvement; less dyspnea; more expansion of the right chest, which was now less flattened. The note was almost wooden to about the second rib. Breath sounds were amphoric without rales. Heart was still displaced.

November 27. The right chest showed improvement. There was now hyperresonance over the front and into the axilla, with good vocal fremitus, but the breath sounds were still distant.

November 30, 1917. The right chest was entirely clear to percussion; the breath sounds were normal; there was full expansion and the heart had retuned to normal position. X-ray showed lung to be entirely clear.

Figs. 4, 5 and 6 show the condition at different stages. (Fig. 4) the shadowed right side with practical disappearance of the heart shadow into the right: viewed from the back.

Fig. 5. Another plate at a later date in which with the dense shadow on the right some suggestion of the mediastinum and heart are appearing to the left (from back).

Fig. 4.—Case I (from behind). Massive collapse of the right lung following appendectomy. The heart shadow has practically disappeared into the density of the right side. Signs on the right side were those of consolidation.

Fig. 5.—Case I (from behind). From the same case, a few days later. The heart shadow and the mediastinum appearing at the left.

Fig. 6. The resolving of the condition on the right side, the reappearance of the shadow of the mediastinum to the left, a margin of the collapsed lung area to the right. Expanding lung to the right is suggested by the picture rather than a pneumothorax. Patient went out with the chest in a completely resolved condition, heart in place.

Fig. 6.—Case I (from behind). The condition in resolution. Heart shadow to the left; distinct line of collapsed lung on the right, with resolving condition of the lung beyond. The final picture in this case showed a complete restoration of thoracic conditions. All pictures taken with the patient in recumbent position.

Case II.—*An acute appendix inflammation. Operation: removal of inflamed appendix; no abscess formation found; ether anesthesia.* On the day following the operation a suddenly developing dyspnea took place and the patient was seen to be in great distress. There was fever, cough and mucoid expectoration; cyanosis was marked and pulse was rapid.

Inspection showed that the left chest was completely fallen in, was not expanding and that the heart was well drawn over to the left side the impulse being seen almost in the axillary line; the whole chest was solidly dull, had increased vocal fremitus but yielded very faint sounds, as if no air was passing into the lung or chest. In a few hours symptoms lessened and by the next day the patient was comfortable, though the chest remained solid. No fluid was found on puncture; the breath sounds became clearly tubular; expansion and beginning resonance were found after forty-eight hours. By the end of the week the heart was well in place and only such signs as an impaired percussion note, limited expansion

and crackling rales were to be found; there was no *x*-ray plant in operation during this patient's illness.

Case III.—*Collapse of the lung following appendectomy.* Willett D., No. 95544, Heavy Battery, R. G. A., aged twenty-six years. Admitted to No. 1 Canadian General Hospital on October 5, 1917, with a history of pain in the right iliac fossa for five days; no vomiting; no diarrhea; no headache. Anorexia was complained of and there was some fever. Patient looked ill; tongue was coated; abdomen looked slightly distended; there was definite resistance and tenderness over McBurney's point and there was to be felt a tender mass like a thickened intestine. Examination was otherwise very negative, save that there was a very definite suggestion of a diffuse bronchitis in the wheezing bronchi to be heard over the whole chest. The patient was operated upon three days later and a perforated appendix surrounded by a small collection of pus was found. Drainage was instituted. About ten hours later, during the night, the patient had a sudden sharp pain in the right side and developed acute respiratory distress; he was cyanosed, coughing and gasping, and the officer on duty reported that the man was dying; in the morning he was seen to be easier in his condition, and an examination was possible. The right chest was seen to be almost motionless and looked sunken to a pronounced degree; the heart was seen beating to the right of the sternum and could be readily felt; there was no sign of cardiac dulness to the left; on the left side the sounds were harsh, but the chest on this side was resonant; on the right there was complete wooden dulness practically to the clavicle; vocal fremitus was strong; the breath sounds were faint and were distant tubular in their quality. Expansion was very slight. The symptoms moderated quickly; by the end of ten days there had been a gradual return to normal; the expansion was noted as better and the chest looked fuller; percussion gave an almost normal note. The breath sounds remained faint and there had never been the change from faint sounds to real tubular breathing which we had seen in some of the other cases; some pulmonary crepitations remained, but there was resonance almost to the lower lung border behind, where still a small patch of dulness remained. The heart had returned to its normal place and was seen and felt to the left of the sternum.

"Five days later," the note says, "heart in place; breath sounds still fainter on right than on left; scattered rales throughout both lungs."

The *x*-ray pictures of this patient's chest are suggestive to a degree.

Fig. 7, viewed from behind: The right chest solid; no sign of heart or mediastinum to the left.

Fig. 8, viewed from behind: Right lung clearing; mediastinal shadow in evidence to left (no full-size chest plates were in stock at this time; picture take on half-size plate).

FIG. 7.—Case III (from behind). Massive collapse after appendectomy. The disappearance of the heart and mediastinum into the involved right side is complete. There is no suggestion of heart shadow to the left.

FIG. 8.—Case III (from behind). The heart and mediastinum returning to the left as the right lung is reëxpanding. No full-size chest plates were in stock at the time of taking these pictures.

Fig. 9, viewed from the front some days later; lungs practically clear and mediastinum and heart in position.

Fig. 9.—(From the front.)—Complete restoration of heart and mediastinum to their normal position with the lungs practically clear.

Though undoubtedly an unusual clinical condition, yet the histories of the cases reported and the suggestive physical signs recorded make it probable that massive collapse of a lung is something to be thought of during the course of acute pulmonary disorders, after anesthesia, after abdominal operations and in any case with obstruction of the air passages. Its frequent occurrence in association with wounds of the lung is an established fact and called for a revision of our ideas on physical signs, particularly those signs which dealt with displacements of the heart and mediastinum.

The condition being an unfamiliar one, has rarely been looked for in a systematic way. In 250 cases of postoperative pulmonary involvements which I have recently analyzed, there was but one note which said that the heart was in position, yet many acutely developing cases of a unilateral consolidation were being considered and examined.

Frank lobar pneumonia giving outspoken signs of consolidation

within a few hours of an operation must be a condition well out of the ordinary, yet such is the actual finding recorded in many post-operative pulmonary complications; lobular pneumonia with bilateral involvement is the commonly accepted idea of what takes place in the lungs after anesthesia and operation; outspoken consolidations of one lung developing suddenly with exaggerated symptoms of distress and dyspnea are suspicious of a lung collapse.

The acute accidents in connection with the heart and circulation are often suggested by the symptoms. Minor emboli from a wound site may cause the first symptoms of pain and distress by lodging on the pleura and may be a contributing cause of the ensuing collapse; pneumothorax of the sound side may be suspected if the compensating overexpansion fills out the chest wall; the displacement of the heart and mediastinum may be further confusing. "Acute, often sudden onset, with symptoms out of the range of those found in a pneumonia or bronchopneumonia of a few hours' duration, signs of consolidation with drawing of the heart into the consolidation, all occurring in the matter of a few hours, suggest collapse of a lung or lobe."

Many conditions seem to contribute to the production of a collapse of a lung: Paralysis of the diaphragm in diphtheria has long been known to be at times associated with complete collapse of the lower lobes of both lungs; filling of bronchi with secretion would seem to be a likely coincidence in the cases with bronchopneumonia and would be a contributing cause. Upper-lobe collapse in association with paralysis of the muscles of the upper chest has also been described (Pearson Irvine).

Obstruction of the larynx and air passages has been shown to be a direct and precipitating cause, Gairdner's "ball-valve action" of the obstructing object, by which air is pressed out past the obstruction in expiration but cannot return with inspiration, may be the explanation in such cases. The rapidity of the collapse in one case recorded above shows in how few minutes all air can be absorbed from the lungs when an obstruction is complete. A reflex action precipitating an active collapse is assumed by some observers.

Infection, preëxisting or subsequent to operation, inhalation of

saliva and mucus during anesthesia, splinting of the abdomen and diaphragm after an abdominal operation, multiple emboli to the lungs from the site of the wound, may all help in the producing of a collapse of the lung after abdominal operation; pulmonary embolism is a well-recognized postoperative happening; it is more often seen, however, in its rapidly fatal forms and the "minor emboli," so well described by Wharton and Pearson,* are rarely thought of; large emboli rarely if ever cause complete atelectasis,

FIGS. 10 and 11.—(From the front.) Pictures of chests of wounded men taken within a few hours of wounds being received. In Fig. 10, a case of through-and-through wound of the right chest, the signs of a hemothorax are evident and there is but little unaffected lung in evidence. The complete involvement of the unwounded side, giving the dense shadow of consolidation of fluid, is evident. Signs of the hemothorax on the right do not allow the appearance of an unquestioned collapse. The physical signs in this case were marked displacement of the heart to the left, with signs of consolidation throughout the left lung. Case made complete recovery

emboli are at best probably only contributory agents in massive collapse.

Collapse of the lung has been reported as occurring in cases operated on under local anesthesia (Elliott and Dingley). Pre-existing lung infection was in evidence before operation; large wounds of the body away from the chest have shown the same

* Jour. of the Am. Med. Assn., December 2, 1922.

interesting collapse of a lung as a complication (Rose Bradford), suggestive evidence that neither diaphragm nor chest wall play a leading part in all cases of pulmonary collapse.

In the "wounds-of-the-lung" cases another active cause may exist: Free-flowing blood may fill the bronchi; if the man lie on his sound side he might drain into his unwounded lung: "contralateral collapse" might ensue. The proof of the existence of an

Fig. 11.—(From the front.) A much more complete picture of a wound of the right lung giving rise to signs of collapse or consolidation in the left. In this case the bullet had passed through the right chest, leaving singularly few signs of chest involvement. Within a few hours marked urgency and signs of consolidation of the whole left chest, with marked displacement to the left of the heart and mediastinum. As shown by examination, the picture shows a density of the left side and the absence of any sign of the heart to the right.

active collapse, a reflex action, has not come forward; such a reflex, with rapidly occurring variations in the blood supply from the pulmonary artery, something which must take place in an erectile tissue like the lung, is at times assumed. Soltau and J. L. Yates have discussed these conditions.

It seems probable that the thorax accommodates itself very quickly to the condition of collapse, since the majority of the patients seized with the accident recover. In the process of compensation the diaphragm rises, the mediastinum falls in and at times the chest

wall can be seen to have collapsed (Fig. 1), distention of the great veins of the thorax might occur in order to help fill the vacuum. The rising of the diaphragm was seen to perfection in the wounds of the left lung with collapse; a frequent observation in these cases was that though the chest was containing effused blood in quantity, Traube's semilunar area of resonance was still persisting.

Further descriptions of the collapse of the lung as seen in wounds of the chest are hardly called for today; interesting details of this serious complication of a chest wound are given by Rose Bradford[7] and other workers in the World War.[8 9] Two important points may be referred to: In a hemothorax, the collapse of the unwounded portion of a damaged lung, giving the confusing conditions of signs of fluid in excess with but little fluid actually to be found, seemed to be a common happening; one wonders if perhaps in the course of certain cases of consolidations, effusions, infarctions or emboli, acute symptoms rapidly developing, may not mean an added collapse, while the many instances in which were seen collapse of the lung of the side away from the wound, a wound which was often a *mere graze of the chest*, with no lung wound and no blood-spitting, lend support to the idea mentioned above, that some reflex cause may precipitate an active collapse of the lung. (Figs. 10 and 11.)

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DISCUSSION

Dr. F. T. Lord, Boston: Thus far the recognition of massive collapse of the lung has been confined, as in Dr. Gwyn's cases, to the more striking and isolated examples of collapse, and for the most part to postoperative and surgical cases. Pulmonary collapse is a frequent and important accompaniment of many conditions and thus under almost daily observation by clinicians. Consider, for example, the minor degree of collapse in the dependent parts of the lung in patients long abed, the contraction or compression of the lung in the neighborhood of pleural tumors, pneumothorax, pleural and pericardial effusions, and the elevation of the diaphragm with tympanites, ascites or subdiaphragmatic abscess. In such conditions recognition of the physical signs of collapse is an important element in a correct diagnosis. More extensive collapse is a striking feature of bronchostenosis, especially from the presence of tumor or foreign body in the bronchi. These types are well known and need mention here only to bring them into consideration with the massive collapse under discussion. But it is not, I think, sufficiently recognized that varying degrees of pulmonary collapse are not uncommonly part of the picture also in suppurative pulmonary processes and in pneumonia, both broncho- and lobar. Such signs as relative dulness, diminished breathing, voice, whisper and tactile fremitus, usually associated with moist rales, are common at the posterior inferior part of the lung in the presence of pulmonary abscess developing at the corresponding root of the lung. It is a common mistake to regard the signs at the base as the essential lesion and to overlook an area of dulness higher up in the back in the region of the root until the *x*-ray discloses the presence of an area of increased density in this region. But such signs at the base are with difficulty differentiated from bronchopneumonia unless there is at the same time displacement of the heart toward the affected side. We have, however, had the experience of noting with abscess not due to foreign body marked displacement of the heart toward the affected side both on physical and *x*-ray examination and its later return to normal position. Cardiac dislocation toward the affected side may be taken in such cases as an indication of massive lung collapse in the absence of pleural or pulmonary pathology on the opposite side.

In the presence of pneumonia developing at the root, as frequently happens, there are often signs consistent with collapse at the corresponding posterior inferior aspects of the lung. Such signs are usually regarded as an indication of infiltration or a complicating pleural fluid when found in connection with obvious signs of consolidation at the region of the root, but negative aspiration makes pleural fluid unlikely and in certain cases cardiac dislocation toward the affected side indicates that massive collapse is the correct explanation. In reviewing my records in 558 cases of pneu-

monia personally examined, I find that there are 14, or 2.5 per cent, in which the heart was displaced toward the side of the pneumonia. In these cases the absence of signs of pleural fluid or air on the opposite side indicates that the cardiac dislocation is attributable to massive collapse. In 2 of the 14, pleural fluid was demonstrated on the affected side while the heart was still displaced toward that side. These 14 patients ranged from fourteen to seventy-five years of age. Seven were from fourteen to seventeen. The heart returns to normal position during the course of the disease. Confirmation of the displacement of the heart and its return is established by *x*-ray examination. The displacement noted in pneumonia has not exceeded 3 cm. in any case. Nine of the cases were classed as lobar and 5 as bronchopneumonia. In contrast to the severity of the accompanying symptoms in Dr. Gwyn's cases the pulmonary collapse in the cases referred to above developed insidiously.

In explanation of massive collapse in connection with these pulmonary destructive lesions and in lobar and bronchopneumonia the suggestion may be offered that partial or complete bronchial occlusion is of inflammatory origin and occurs in the air passages passing through or adjacent to the process with rapid absorption of air in the parts supplied by the occluded passages and that pulmonary collapse arises in consequence. Only the collapse of relatively large areas leads to cardiac dislocation.

Dr. Gwyn (closing): I am glad to hear Dr. Lord mention effusion as one of the causes of the sudden collapse of the lung. The heart might be drawn over to the side on which the effusion existed if an expanded part of the lung should suddenly collapse.

During the War we often made the mistake of thinking that the chest would be found full of blood on the wounded side when what actually was found was that a small effusion had taken place, the whole lung had collapsed quickly and the chest had become solid as if containing a large effusion. Repeated puncture in the chest in this type of case rarely gave more than a few drams or an ounce or two of blood, and we soon came to recognize that in these cases collapse of the lung more than the fluid in the pleura was responsible for the symptoms and physical signs.

THE USE OF RADIUM RADIATIONS IN THE TREATMENT OF TONSILS: A FURTHER REPORT[1]

By FRANCIS H. WILLIAMS, M.D.

The prevalence of abnormal conditions in the tonsils and the serious results that may arise from them in widely separated portions of the body, certain of them so serious that tonsillectomy has been necessary, are incentives to study other methods of treatment, and I present here in abstract a paper read by title at this meeting, that will appear in full in *The American Journal of the Medical Sciences,* which gives a part of my experience with one method.

By this method radium is applied in a container directly to the tonsil, the amount and quality of the radiations being controlled by means of suitable diaphragms and filters, and the parts to be treated illuminated by an electric lamp attached to the rod carrying the container. The treatment may be so moderate as to produce no discomfort in the throat or, if desired, so vigorous as to cause some irritation there for a few days. A good first dose for an adult, when 38 mg.[2] of radium element are used, the filter of aluminum being 0.58 mm. thick, is about ten minutes for each tonsil. Subsequent doses should be smaller or larger, as the conditions require. With the same amount of radium, the same diaphragm and filter, and the same length of exposure, a given treatment can be repeated with exactitude. A good initial

[1] Treatment of Hypertrophied Tonsils and Adenoids by Radium: A Preliminary Statement, Boston Med. and Surg. Jour., March 10, 1921, clxxxiv, 256–257. The Treatment of Tonsils by Radiations from Radium Salts Instead of Operation: 101 Cases, Trans. Assn. Am. Phys., 1922, xxxvii, 204–212; Boston Med. and Surg. Jour., 1922, clxxxvii, 412–416. Traitement de l'hypertrophie amygdalienne par la curiethérapie; Paris méd., 1923, xlvii, 110–113.

[2] With the experience I have now had in the treatment of tonsils I feel justified in using larger amounts of radium with the object of shortening the length of the exposures and the duration of the whole treatment.

treatment for children, with the same amount of radium and filter described above, is usually about five minutes. For delicate children one exposure only of even five minutes may be followed by such improvement that further treatment may be more easily given. A 2 per cent solution of cocaine may be used, if necessary, to desensitize the throat.

The 66 cases considered in this paper include 11 cases of enlarged tonsils, 21 of tonsillitis, 13 of tonsillitis and arthritis,[3] 12 of arthritis, 8 of previous tonsillectomy[4] (4 of these had had tonsillitis after this operation) and 1 of tonsillotomy. The striking fact about these cases was the improvement in the well-being of nearly all, beginning sometimes even before there was any discharge from the tonsils; the increase in weight in some, in amounts varying from 10 to 17 pounds; freedom from attacks of tonsillitis, except in 3 cases, from the beginning of treatment, and marked relief from arthritis, especially in acute cases.

How far it is desirable or necessary to reduce the tonsils in order to insure no further attacks of tonsillitis, or of arthritis of which these organs are the source, is yet to be determined. In some cases after the treatment was completed no tonsil was seen when a curtain (the edge of which was directed backward and which was attached near the top of the anterior pillar and reached to near the base of the posterior pillar) was drawn aside, but when the finger was passed around the curtain a flattened mass about as large as a good-sized pea was felt near the anterior pillar on the side toward the cheek. In such cases I should not expect that there would be any further trouble, but when the tonsils are not

[3] About two years ago it occurred to me that radium treatment of the tonsils might be beneficial in scarlet fever, and the continued good effects of this remedy in cases of acute tonsillitis locally, and in arthritis and other diseased conditions, the source of which is in the tonsils, has strengthened me in this theory. This treatment might mitigate or prevent the nephritis, for example, that may accompany scarlet fever and, if given early, there might be no rash. It may even be that the cause of scarlet fever is harbored, among other places, in the tonsils, and that radium by promoting drainage might dislodge it. (This might give opportunity for search in the discharge for the cause of scarlet fever). I have sought, but have not as yet had an opportunity of testing this use of radium.

[4] In this connection the following statement is pertinent: "Study of more than 30,000 patients from various sources one to four years after operation shows permanent results in only about one-half of the total number" (Laura A. Lane, M.D., Associate Attending Surgeon, Eye, Nose and Throat Department, Minneapolis General Hospital, Minnesota Med., 1923, vi, 97–104.)

so reduced it remains to be seen after how long an interval, if at all, trouble will occur. Should it do so, and further radium treatment giving no relief, operation should be thought necessary, it could be done more easily and safely on account of the previous treatment because the tonsils would be smaller, their outlines more defined and the operating field cleaner; probably also there would be less risk of hemorrhage. Thus far I have not found operation necessary, but it will be instructive to note what, if any, improvement takes place after an operation following radium treatment beyond that accomplished by the radium.

Radium is a valuable therapeutic agent not only for the treatment of faucial tonsils, but also for other lymphoid tissue in the throat. I do not recall any remedy that can be made so useful in laryngology as radium. When treating the tonsils the conditions in the pharynx should not be overlooked, as they may be such that radium can afford relief there also. Radium is especially helpful in cases in which tonsillectomy is contraindicated on account of cardiac disease or pulmonary tuberculosis, for example. In the latter case particularly its use may remove a serious handicap. It is also useful for treating the tonsils after tonsillectomy instead of a second operation, and it is well that this should be done before regeneration takes place. It is of interest to note that after radium treatment there may be little, if any, lymphoid tissue remaining. This is not the case with incomplete tonsillectomy. There need be no delay in the use of radium on account of the season of the year, or because of acute conditions in the tonsils themselves, or of an acute stage in diseases that have their source in the tonsils. This method of using radium is adapted to the treatment of the pharynx and the region around the Eustachian tube, for example, as well as of the faucial tonsils. There have been no harmful results from the use of this method in 200 cases that I have treated, the first of them more than two years ago. Time and experience will determine the limitations of this remedy and the duration of the results obtained: This use of radium will, I believe, give us new points of view from which to study the problem of how best to care for the tonsils.

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